Quantum metrology and its application in biology

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Abstract

Quantum metrology provides a route to overcome practical limits in sensing devices. It holds particular relevance in biology, where sensitivity and resolution constraints restrict applications both in fundamental biophysics and in medicine. Here, we review quantum metrology from this biological context. The understanding of quantum mechanics developed over the past century has already enabled important applications in biology, including positron emission tomography (PET) with entangled photons, magnetic resonance imaging (MRI) using nuclear magnetic resonance, and bio-magnetic imaging with superconducting quantum interference devices (SQUIDs). With the birth of quantum information science came the realization that an even greater range of applications arise from the ability to not just understand, but to engineer coherence and correlations in systems at the quantum level. In quantum metrology, quantum coherence and quantum correlations are engineered to enable new approaches to sensing. This review focusses specifically on optical quantum metrology, where states of light that exhibit non-classical photon correlations are used to overcome practical and fundamental constraints, such as the shot-noise and diffraction limits. Recent experiments have demonstrated quantum enhanced sensing of biological systems, and established the potential for quantum metrology in biophysical research. These experiments have achieved capabilities that may be of significant practical benefit, including enhanced sensitivity and resolution, immunity to imaging artifacts, and characterisation of the biological response to light at the single-photon level. New quantum measurement techniques offer even greater promise, raising the prospect for improved multi-photon microscopy and magnetic imaging, among many other possible applications.

Keywords: Quantum metrology, biology, cell, coherence, quantum correlations, squeezed state, NOON state, shot noise, quantum Fisher
1. Introduction

Fundamentally, all measurement processes are governed by the laws of quantum mechanics. The most direct influence of quantum mechanics is to impose constraints on the precision with which measurements may be performed. However, it also allows for new measurement approaches with improved performance based on phenomena that are forbidden in a purely classical world. The field of quantum metrology investigates the influence of quantum mechanics on measurement systems and develops new measurement technologies that can harness non-classical effects to their advantage.

Quantum metrology broadly began with the discovery that quantum correlated light could be used to suppress quantum shot noise in interferometric measurements, and thereby enhance precision \cite{1}. To this day, the development of techniques to enhance precision in optical measurements remains a primary focus of the field. Such enhancement is particularly relevant in situations where precision cannot be improved simply by increasing optical power, due for example to power constraints introduced by optical damage or quantum measurement back-action \cite{2}. One such situation is gravitational wave measurement, where kilometre-scale interferometric observatories operate with power near the damage threshold of their mirrors, yet still have not achieved the extreme precision required to directly observe a gravitational wave \cite{3}. Biological measurements are another application area which has been discussed from the earliest days of quantum metrology \cite{4, 5, 6, 7}, since biological samples are often highly photosensitive and optical damage is a limiting factor in many biophysical experiments \cite{8, 9, 10}.

Although these applications were recognised in the 1980s, at that time the technology used for quantum metrology was in its infancy and unsuited to practical measurements. Since then, both the technology and theory of quantum metrology has advanced dramatically. This has allowed quantum metrology to be applied routinely in full-scale gravitational wave observatories to achieve unprecedented precision \cite{11, 12, 13}. The advances in quantum metrology technology have also enabled a number of recent biological applications \cite{14, 15, 16, 17, 18} and new biologically relevant measurement technologies. As researchers continue to explore the possibilities of biological quantum metrology, such applications are likely to soon become both
widespread and competitive as they provide practical advantages over classical measurement strategies. This review aims to introduce quantum metrology from the context of biological measurements, and then summarize both the biological applications already achieved and the future potential for the area.

Although quantum metrology is generally considered to have begun in the 1980s, positron emission tomography (PET) has been utilizing entangled photon pairs in imaging since the 1960s [19, 20]. In PET, a radioactive marker undergoes $\beta^+$ decay to produce a positron. The positron annihilates with a nearby electron to produce a high energy entangled photon pair. Since the photons propagate in near-opposite directions, the position of the annihilation event can be estimated to occur along a chord connecting coincident photon detections. With sufficient coincident detection events, a full 3D profile of the radioactive marker density can be reconstructed. This is now used routinely in clinical applications to image cancerous tumours and to observe brain function [21]. PET is a truly non-classical technology, since the correlated photon propagation and coincident detection cannot be fully explained by a classical wave treatment of light.

The development of modern quantum technologies allows non-classical states to be engineered, in contrast to the uncontrolled generation of entangled photons which is used in PET. This allows for a far broader range of applications [14, 15, 16, 17, 18]. Entangled photon pairs have now been applied in tissue imaging [14] and in refractive index sensing of a protein solution [15]; squeezed states of light have been used both to measure dynamic changes [16] and image spatial properties [17] of sub-cellular structure; and single photons have been used to stimulate retinal rod cells, thus allowing the cellular response to single photons to be deterministically characterized [18]. These experiments have demonstrated that with further advances engineered quantum correlations offer the prospect for new capabilities and unrivalled precision in practical biological measurements. Furthermore, numerous technologies have already been demonstrated in non-biological measurements which could soon have important applications in biology. These near-future applications include cellular imaging with both multi-photon microscopy [22, 23] and super-resolution of fluorescent markers [24, 25], enhanced absorption [26] and phase contrast [27, 28] microscopy, and measurement of biomagnetic fields [29].

Although the techniques developed in quantum metrology have the potential to improve measurements quite generally, optical measurements com-
prise the majority of the research to date, and all biological applications of quantum correlations. Consequently, this review will focus primarily on optical quantum metrology techniques. This review begins with a qualitative explanation of quantum noise in optical measurements, which allows a qualitative, but not rigorous, derivation of both the standard quantum limit and the Heisenberg limit (Section 2). It then proceeds to a quantum mechanical description of photodetection, quantum coherence and quantum correlations (Section 3). Section 4 introduces the theoretical tools of quantum metrology for the example case of optical phase measurement, and introduces the commonly used squeezed and NOON states. Following this, Section 5 introduces additional concepts required for an analysis of spatially resolved imaging. Section 6 then describes the unique challenges associated with practical biological experiments, including resolution requirements, optical damage, and the non-static nature of living cells. The experiments which have applied quantum metrology in biology are described in Section 7. Section 8 overviews a range of promising technologies which in future may have important biological applications. Thus far these sections all discuss technologies based on quantum correlated light, though measurement technologies have also been developed which rely on quantum correlated spin states. Section 9 provides a brief overview of spin-based quantum metrology experiments that hold promise for future biological applications. Finally, Section 10 concludes the review with a broad summary of the potential of quantum metrology for biological measurements in the near future.

2. Semi-classical treatment of optical phase measurement

The measurement process quite generally involves the preparation a probe, its interaction with a system of interest, and then read-out of the probe to extract relevant information about the system. For instance, phase measurements typically involve generating an optical field with a laser, propagating it though an interferometer and measuring the power in the two output ports to estimate the phase shift $\phi$ applied within one arm of the interferometer (see Fig. 1). More generally, the probe need not be laser light; optical measurements can also be carried out any state of light including thermal light [30] or non-classical states of light [2], while non-optical measurements can be carried out with a wide range of probes such as atom waves [31], spin states of atoms [32], or mechanical states of a cantilever [33]. In the field of quantum metrology, the influence of the input state on the achievable preci-
Figure 1: A classical analysis of a phase sensing experiment based on a Mach-Zehnder interferometer. An incident optical field $E_0$ is split at the input port of the interferometer by a beamsplitter with transmission $\eta$. A differential phase shift $\phi$ is then applied between the fields in the two arms. The phase shift is estimated by recombining the fields and measuring the relative optical powers at the two output ports.
gates through a Mach-Zehnder interferometer, with the field in the reference arm acting as a phase reference. The field in the signal arm experiences a phase shift $\phi$ from its interaction with a sample, which is estimated from intensity measurements at the two interferometer outputs (Fig. 1). Following a classical treatment of this problem, and taking the case where the two beam splitters in the interferometer each have 50% reflectivity and no absorption, the fields that reach the detectors are given by

$$E_A(t) = \frac{1}{2} (1 + e^{i\phi}) E_0(t)$$

$$E_B(t) = \frac{1}{2} (1 - e^{i\phi}) E_0(t),$$

where $E_0(t)$ is the incident optical field. Each field is then detected with a photodiode. Quantized photocurrents $n_A(t)$ and $n_B(t)$ are produced as valence band electrons are independently excited into the photodiode conduction band, with probability proportional to the optical intensity. As such, the mean photocurrent is determined by the intensity ($\langle n(t) \rangle \propto |E(t)|^2$), though the photocurrent also fluctuates with random statistics. In a quantum treatment of photodetection, each photoelectron is excited by a single photon (see Section 3). Consequently, the photocurrents $n$ can equivalently be thought of as the photon occupation of the detected fields. Evaluating the detected intensities, one finds that

$$\langle n_A(t) \rangle = \frac{\langle n_0(t) \rangle}{2} (1 + \cos \phi)$$

$$\langle n_B(t) \rangle = \frac{\langle n_0(t) \rangle}{2} (1 - \cos \phi).$$

Information about $\phi$ can be extracted from the difference photocurrent, which has a mean value of

$$\langle n_A(t) - n_B(t) \rangle = \langle n_0(t) \rangle \cos \phi.$$ 

The phase sensitivity is optimal when $\phi = (m + 1/2)\pi$ where $m \in \mathbb{Z}$, since this maximises the derivative of the difference photocurrent with respect to a small change in $\phi$. Interferometers are generally actively stabilised to ensure operation near one of these optimal points. For small displacements about this point, the phase shift $\phi$ is given to first order as

$$\phi = \frac{\langle n_A(t) - n_B(t) \rangle}{\langle n_0(t) \rangle} - \frac{\pi}{2}. $$
Consequently, the relative phase may be estimated as
\[ \phi_{\text{estimate}}(t) = \frac{n_A(t) - n_B(t)}{\langle n_0(t) \rangle} - \frac{\pi}{2}. \] (5)

The statistical variance of the phase estimate is then given by
\[ V(\phi) = \frac{V(n_A) + V(n_B) - 2 \text{cov}(n_A, n_B)}{\langle n_0 \rangle^2}, \] (6)

where \( V(x) = \langle x^2 \rangle - \langle x \rangle^2 \) is the variance of the variable \( x \), and the covariance \( \text{cov}(x, y) = \langle (x - \langle x \rangle)(y - \langle y \rangle) \rangle \) quantifies the correlations between the variables \( x \) and \( y \). In our semi-classical treatment, photo-electrons are generated through a stochastic random process at each photodetector. In the limit that the optical fields are stationary in time, the detection events at each detector are uncorrelated (\( \text{cov}(n_A, n_B) = 0 \)) and have fixed probability. This results in Poissonian statistics, such that the variance of each photocurrent is equal to its mean, \( V(n_i) = \langle n_i \rangle \) with \( i \in \{1, 2\} \). The number fluctuations at each detector are then given by \( V(n_A) = V(n_B) = \frac{1}{2} \langle n_0 \rangle \). As discussed in Section 4.2, this prediction of Poissonian statistics is consistent with a fully quantum treatment of a coherent state, which is the state generated by a perfectly noise-free laser. Substituting for the photocurrent variances and covariance in Eq. (6), the achievable phase precision is given by
\[ \Delta \phi_{\text{SQL}} = \sqrt{V(\phi)} = \frac{1}{\sqrt{\langle n_0 \rangle}}. \] (7)

Even though the approach used here is semi-classical and treats the optical electric field as a perfectly deterministic quantity, Eq. (7) reproduces the standard quantum limit for phase measurements, which quantifies the best precision that can be reached in phase measurement without the use of quantum correlations. As discussed in Section 4.2, the standard quantum limit can be achieved using coherent states. In fact, coherent states achieve the best precision possible without quantum correlations for many forms of measurement, not just phase estimation [2]. Consequently, the sensitivity achievable using coherent light of a given power generally provides an important benchmark for quantum metrology experiments.

Examination of Eq. (6) suggests that precision can be improved if the detection events are correlated, such that \( \text{cov}(n_A, n_B) > 0 \). Fluctuations
in the intensity can provide such correlations, though this also increases the photon number variances $V(n_A)$ and $V(n_B)$ so that precision is not improved.

The above derivation only assumes quantization in the photocurrent which provides the electronic record of the light intensity. As such, the limit of Eq. (7) follows if we consider either a perfectly noiseless optical field which probabilistically excites photoelectrons, or a quantized field with each photon exciting a single electron. Violation of this limit, however, requires electron correlations in the detected photocurrents which cannot follow from probabilistic detection, and therefore requires a quantum treatment of the optical fields [34].

2.2. Variations on the quantum limit

2.2.1. The quantum noise limit

The above analysis neglects the possibility of optical loss or inefficient detection. It is straightforward to include such imperfections, since interferometric phase measurement is a linear process. As a consequence, balanced loss introduced in the arms of the interferometer has the same effect as loss introduced before the interferometer input. Within this semi-classical analysis, loss acts only to reduce the effective input optical power, though a more detailed analysis is required in the general case with non-classical states of light (see Section 4.5). If the input light is detected with efficiency $\eta$, shot noise limits the optimal achievable precision to

$$\Delta \phi_{\text{QNL}} = \frac{1}{\sqrt{\eta \langle n_0 \rangle}}.$$ (8)

This is referred to as the quantum noise limit, and quantifies the limit to precision achievable without quantum correlations in the presence of inefficiencies. Since any real experiment contains inefficiencies, the quantum noise limit is generally achievable with coherent laser light, while the standard quantum limit is not. Quantum metrology experiments often compare their achieved precision to the quantum noise limit, as violation of this limit proves that quantum resources have enabled improved precision. The standard quantum limit provides a more stringent bound, which defines the precision that is achievable without quantum correlations in an apparatus with no loss and perfect measurement. Violation of this limit therefore proves that the experiment operates in a classically unachievable regime. The standard quantum limit and quantum noise limit are generally used in different contexts, with continuous measurements on bright fields often compared to the
quantum noise limit \([35, 16, 29, 36, 12]\), and photon counting measurements typically compared to the standard quantum limit \([15, 37, 38]\).

Although the quantum noise limit is widely used, there is no clear consensus as to its name. It is most often referred to as either the quantum noise limit \([35, 16, 36]\) or the shot noise limit \([13, 26, 29]\), often interchangeably \([12]\), though other names are also used \([39, 40, 41]\). It is also important to note that the phrase “standard quantum limit” carries two distinct meanings in different communities. While much of the quantum metrology community uses the definition introduced here, the optomechanics community defines the standard quantum limit as the best sensitivity possible with arbitrary optical power, which occurs when quantum back-action from the measurement is equal to the measurement imprecision \([2]\).

### 2.2.2. Power constraints

As can be seen from Eqs. (7) and (8) the phase measurement precision can in principle be enhanced arbitrarily by increasing the incident optical photon number \(\langle n_0 \rangle\). Consequently, quantum limits on precision are only relevant in circumstances where the optical power is constrained.

Given an experimental constraint on the total power \(\langle n_0(t) \rangle\) due for example to limitations in laser output or detector damage thresholds, Eq. (7) describes the quantum limit to precision. In many other experiments, however, the constraint is instead placed on the power incident on the sample, due for example to the optical damage threshold of the sample. In this case the precision can be improved by unbalancing the interferometer such that the reference arm carries more power than the signal arm. This suppresses the noise contribution from photon fluctuations in the reference arm, thereby improving the precision achievable for a fixed power at the sample. A similar treatment to that given above shows that the standard quantum limit in this case is

\[
\Delta \phi_{SQL} = \frac{1}{2\sqrt{\langle n_{\text{sig}} \rangle}},
\]

where \(n_{\text{sig}}\) is the photon number in the signal arm. Of the possible constraints on power, this latter one is generally more relevant to biological problems, where the sample is often susceptible to photo-induced damage and photochemical intrusion (see Section 6.4). Despite the important distinction between these limits, they can usually only be distinguished by the context in which they are found, as they are both conventionally given the same name. Within this review, the differing limits can be distinguished by...
the dependence on the photon number; the total power is designated by $n_0$, while the signal power is designated by $n_{\text{sig}}$.

Thus far the discussion has centred entirely on interferometric phase measurements. A similar semi-classical analysis can also be performed to find the quantum limit for most other optical measurements. For instance, Poissonian detection statistics also introduces noise to amplitude or intensity measurements, thus setting a lower limit to precision. Although the exact form of the quantum limits can depend on the type of measurement, the precision achievable with coherent light is almost always used as a benchmark in quantum metrology experiments.

2.3. The Heisenberg Limit

The standard quantum limit derived above cannot be violated with purely probabilistic photon detection. However, as can be seen in Eq. (6), the presence of correlations ($\text{cov}(n_A, n_B) > 0$) between the output photocurrents of the interferometer provides the prospect to suppress statistical noise and therefore improve the measurement precision. In particular, the two detected fields could in principle be entangled such that photon detection events are correlated, suppressing the statistical variance in the difference signal. Taken to its extreme, it can be conceived that perfect entanglement may allow the elimination of all statistical noise in Eq. (6). In this case, the phase precision would only be limited by the requirement that $n_A$ and $n_B$ be integers. A phase shift can only be resolved if it changes the difference signal $n_A - n_B$ by at least one photon. Under a constraint on total power, this limits the possible precision to

$$\phi_{\text{Heisenberg}} \geq \frac{1}{\langle n_0 \rangle},$$

(10)

Once again, this semi-classical derivation reproduces an important and fundamental result. Eq. (10) is generally referred to as the Heisenberg limit, and is the absolute limit to precision possible in a phase measurement using exactly $n_0$ photons, as discussed in more detail in Section 4.4. It is often described as the lower limit on the precision achievable using any quantum state [2]. In fact, it is possible to outperform this limit by a small factor using states with indeterminate total photon number, though no phase estimation scheme has been found that achieves superior scaling with the photon number (see Section 4.4). For completeness, we note nonlinear parameters can in principle be estimated with scaling superior to $1/\langle n_0 \rangle$ [12, 13]; however, it
is not currently clear what benefits such approaches might offer in biological applications, and they will not be discussed further in this Review.

Notice that the Heisenberg limit scales faster in $\langle n_0 \rangle$ than the standard quantum limit. In principle, this promises a dramatic improvement in precision. For instance, a typical 1 mW laser has a photon flux of around $10^{16} \, s^{-1}$. If the Heisenberg limit could be reached with this photon flux, it would be possible within a one second measurement time to achieve a phase sensitivity $10^8$ times superior to the best sensitivity possible without quantum correlations. Unfortunately, as it turns out, entanglement tends to become increasingly fragile as the number of photons involved increases which places a prohibitive limitation on the absolute enhancements that are possible (see Section 4.5).

## 3. Quantum coherence and quantum correlations

A quantum treatment of photodetection and optical coherence was first performed by Glauber and Sudarshan in Refs. [45, 46]. Following a quantum treatment of the optical fields, one finds that there are some optical phenomena which exhibit classically forbidden behaviour, such as two-photon interference in a Hong-Ou-Mandel (HOM) interferometer [44] (see Fig. 2). Such non-classical phenomena rely on quantum correlations that can be used to surpass quantum limits to measurement such as the quantum noise limit and standard quantum limit introduced above. Here we briefly summarise concepts in quantum coherence that are relevant to quantum metrology.
3.1. **Quantum treatment of the electric field**

In a full quantum treatment of light, the deterministic classical description of the optical electric field introduced earlier must be replaced with an operator description. The electric field is decomposed into a sum of contributions from a complete set of orthonormal spatial modes

\[
\hat{E}(t) = i \sqrt{\frac{\hbar \Omega_m}{2 \epsilon_0 V_m}} \sum_m \left[ \hat{a}_m u_m(r) e^{-i \Omega_m t} - \hat{a}_m^\dagger(t) u_m^*(r) e^{i \Omega_m t} \right],
\]

where \( u_m(r) \), \( \Omega_m \), and \( V_m \) are, respectively, the spatial mode function, frequency, and volume of mode \( m \); and \( \hat{a}_m \) is an annihilation operator which, when acted upon an optical field, removes one photon from mode \( m \). It is straightforward to show that \( \langle |\hat{E}(t)|^2 \rangle \propto \sum_m \langle \hat{n}_m \rangle \), where \( \hat{n}_m = \hat{a}_m^\dagger \hat{a}_m \) is the photon number operator for mode \( m \). Therefore, similarly to our previous classical description, \( \langle |\hat{E}(t)|^2 \rangle \) is proportional to the total mean photon number in the field.

3.2. **Quantum treatment of photodetection**

Following the approach of Glauber [45], the process of photodetection can be viewed as the annihilation of photons from the optical field, with corresponding generation of photoelectrons that can be amplified to generate a photocurrent. Annihilation of one photon collapses the state of the optical field from its initial state \( |i\rangle \) into a new state, defined by the initial state acted upon by the annihilation operator \( \hat{a} \)

\[
|i\rangle \rightarrow \hat{a} |i\rangle,
\]

where for simplicity, here and henceforth we limit our analysis to only one spatial mode of the field and drop the subscript \( m \). Fermi’s Golden Rule tells us that the transition rate to an arbitrary final state \( |f\rangle \) due to photon annihilation is proportional to

\[
R_{i \rightarrow f} \propto |\langle f | \hat{a} |i\rangle|^2.
\]

Since the optical field is destroyed in the photodetection process, we are ultimately uninterested in the transition rate to a specific final state, but rather the overall decay of the field. This is given by the sum over all possible
final states

\[
R^{(1)}(t) = \sum_f R_{i \rightarrow f} \tag{14}
\]

\[
\propto \sum_f |\langle f|\hat{a}|i\rangle|^2 = \sum_f \langle i|\hat{a}^\dagger f\rangle\langle f|\hat{a}|i\rangle = \langle i|\hat{a}^\dagger \hat{a}|i\rangle = \langle \hat{a}\rangle = \langle \hat{n} \rangle \tag{15}
\]

where \( \hat{n} \) is the photon number operator. We see, as expected, a direct correspondence to the classical case where the photon number in the field \( n(t) \) is viewed as a classical stochastic process, with the rate at which photons are detected being proportional to the photon number in the field.

### 3.3. Higher order quantum coherence

Let us now consider a second order process where two photons are annihilated. In general, the annihilation events can occur at distinct locations in space and time. However, here we restrict our analysis to co-located events to display the essential physics in the simplest way. In this case

\[
|i\rangle \rightarrow \hat{a}\hat{a}|i\rangle. \tag{16}
\]

Repeating a similar calculation as that performed above for single photon annihilation events using Fermi’s Golden Rule, we find that the rate of two-photon detection is proportional to

\[
R^{(2)}(t) \propto \langle \hat{a}^\dagger \hat{a}^\dagger \hat{a}\hat{a} \rangle \tag{17}
\]

\[
= \langle \hat{n}^2 \rangle - \langle \hat{n} \rangle, \tag{18}
\]

where we have used the commutation relation

\[
[\hat{a}, \hat{a}^\dagger] = \hat{a}\hat{a}^\dagger - \hat{a}^\dagger \hat{a} = 1. \tag{19}
\]

We see that, due to the non-commutation of the annihilation operators the rate of two-photon detection is fundamentally different than would be predicted for a classical stochastic variable \( n(t) \), including the additional term \( -\langle \hat{n} \rangle \).

To quantify the second order coherence it is conventional to define the normalised second order coherence function

\[
g_{11}^{(2)} = \frac{R^{(2)}(t)}{R^{(1)}(t)^2} = \frac{\langle \hat{n}^2 \rangle}{\langle \hat{n} \rangle^2} - 1 + \frac{V(\hat{n})}{\langle \hat{n} \rangle^2} - \frac{1}{\langle \hat{n} \rangle}, \tag{20}
\]

\[13\]
where \(V(\hat{n}) = \langle \hat{n}^2 \rangle - \langle \hat{n} \rangle^2\) is the variance of \(\hat{n}\) and the sub-script ‘11’ is used to indicate that the annihilation events are co-located in space and time. In the more general case of non-coincident annihilation, both in time and space, the second order coherence function can be easily shown to be

\[
g^{(2)}_{12} = \frac{\langle \hat{a}^\dagger_1 \hat{a}^\dagger_2 \hat{a}_2 \hat{a}_1 \rangle}{\langle \hat{n}_1 \rangle \langle \hat{n}_2 \rangle},
\]

where the subscript \(j \in \{1, 2\}\) is used to label an annihilation event at some spatial location \(r_j\) and time \(t_j\). When the annihilation events are spatially co-located \((r_1 = r_2)\), this expression reduces to the well known \(g^{(2)}(\tau)\) with the substitution \(t_1 \rightarrow t\) and \(t_2 \rightarrow t + \tau\)

\[
g^{(2)}(\tau) = \frac{\langle \hat{a}^\dagger(t) \hat{a}^\dagger(t + \tau) \hat{a}(t + \tau) \hat{a}(t) \rangle}{\langle \hat{n}(t) \rangle \langle \hat{n}(t + \tau) \rangle}.
\]

Higher order coherence functions may be defined analogously to Eq. (21) for annihilation events involving more than two photons (see Ref. [47] for further details).

### 3.4. Classically forbidden statistics

It is illuminating to compare the second order correlation functions in Eq. (20) and (21) to those obtained by modelling the photon number \(\hat{n}\) as a classical stochastic process \(n(t)\) described by a well defined probability distribution \(|E(t)|^2\). For a field which can fluctuate in time, a classical treatment finds that \(R^{(1)} \propto \langle |E|^2 \rangle\) and \(R^{(2)} \propto \langle |E|^4 \rangle\). The classical second order coherence function is then

\[
g^{(2)}_{11, \text{classical}} = \frac{\langle |E|^4 \rangle}{\langle |E|^2 \rangle^2} = 1 + \frac{V(|E|^2)}{\langle |E|^2 \rangle^2} = 1 + \frac{V(n)}{\langle n \rangle^2}.
\]

Similarly, the two-point correlation function would classically be given by

\[
g^{(2)}_{12, \text{classical}} = \frac{\langle n_1 n_2 \rangle}{\langle n_1 \rangle \langle n_2 \rangle}.
\]

As pointed out by Glauber [45], there exist rigorous bounds on the values that these classical coherence functions can take. Firstly, since \(V(n) \geq 0\) it is immediately clear from Eq. (23) that

\[
g^{(2)}_{11, \text{classical}} \geq 1.
\]
A classical field can only saturate this limit if it is perfectly noise-free. By inspection of Eq. (20) it is clear that a quantum mechanical field can violate this limit. Similarly, the Cauchy-Schwarz inequality \( \langle n_1 n_2 \rangle^2 \leq \langle n_1^2 \rangle \langle n_2^2 \rangle \) can be applied to Eq. (24) to show that

\[
g^{(2)}_{12, \text{classical}} \leq \left[ g^{(2)}_{11, \text{classical}} g^{(2)}_{22, \text{classical}} \right]^{1/2}.
\]  

(26)

No process with a well defined classical probability distribution can exceed either of these bounds. However, both may be violated with a non-classical field due to the additional term in Eq. (20) which acts to reduce the second order coherence function in co-incident detection. Higher order coherence functions exhibit similar classical bounds, which also may be violated with non-classical fields. Violation both indicates that the field cannot be described fully by a classical probability distribution (and consequently is ill-behaved in phase space in the Glauber–Sudarshan \( P \)–representation [48]), and is an unambiguous signature that quantum correlations are present. Importantly, the inability to describe such non-classical states via a classical probability distribution provides the prospect for measurements whose performance exceeds the usual bounds introduced by classical statistics.

### 3.5. Photon bunching and anti-bunching

The second order coherence function quantifies pair-wise correlations between photons in an optical field. If no pair-wise correlations are present \( g^{(2)}(\tau) = 1 \) for all \( \tau \). If the average intensity fluctuates, due, for example to temperature fluctuations in a thermal source, temporally co-incident photons are more likely at times of high intensity. This is known as photon bunching, and is quantified by a second order coherence function for which \( g^{(2)}(\tau) < g^{(2)}(0) \). Photon co- incidences can also be suppressed, which is known as photon anti-bunching and characterised by \( g^{(2)}(\tau) > g^{(2)}(0) \). Photon anti-bunching occurs naturally in atomic emission, since an atom is a single-photon emitter. Such a system enters the ground state upon emission of a photon, and must first be excited before it can emit another photon. A non-classical field with \( g^{(2)}(0) < 1 \) (see Eq. (23)) must also exhibit anti-bunching, since at sufficiently long delays \( \tau \) any correlations between photons must decay away with \( g^{(2)}(\tau) \) approaching unity. Photon bunching and anti-bunching, and their corresponding second order coherence functions are illustrated in Fig. 3.
Figure 3: Photon statistics can be formally quantified with higher order correlation functions, such as $g^{(2)}(\tau)$ (see Eq. (22)), as shown here. The example profiles here correspond to (upper red) thermal light with photon bunching ($g^{(2)}(\tau) < g^{(2)}(0)$), (blue) coherent light with $g^{(2)}(\tau) = 1$, and (bottom green) anti-bunched light ($g^{(2)}(\tau) > g^{(2)}(0)$).

3.6. Phase space representations of optical states

Similarly to classical fields, it is often convenient to represent quantum fields as a vector in phase space. However, there exist fundamental differences in the phase space representations of classical and quantum fields. Classical fields may, in principle, be noiseless and represented as a deterministic vector in phase space. Furthermore, in the presence of noise they can be represented as a positive-definite well behaved probability distribution. As we will see in this Section, quantum fields, by contrast, exhibit a fundamental minimum level of phase space uncertainty due to the well known Uncertainty Principle, and have quasi-probability distributions (the quantum analog of a classical probability distribution) that can be badly behaved and even negative over small regions of phase space. Several different but closely related quasi-probability distributions are commonly used to describe quantum fields, including the $P$-representation\[49\], the $Q$-representation\[50\], and the Wigner representation\[51\]. In this review we focus on the Wigner representation, since it is mode analogous to a usual classical probability distribution. For simplicity, we avoid a mathematical definition of the Wigner representation, but rather discuss qualitative aspects of the distribution.

\[1\]It can be shown that there is a one-to-one correspondence between a badly-behaved $P$-representation and the existence of non-classical correlations discussed in the previous Section\[48\].
3.6.1. Optical amplitude and phase quadratures

The amplitude and phase quadratures which form the axes of the Wigner representation are the quantum mechanical analog of the real and imaginary parts of a classical electric field. They may be defined in terms of the creation and annihilation operators as

\[ \hat{X} = \hat{a}^\dagger + \hat{a}^\dagger \],
\[ \hat{Y} = i (\hat{a}^\dagger - \hat{a}) \].

(27)

(28)

Using the boson commutation relation given in Eq. (19), it is possible to show that the optical amplitude and phase quadratures do not commute, and satisfy

\[ [\hat{X}, \hat{Y}] = \hat{X}\hat{Y} - \hat{Y}\hat{X} = 2i \].

(29)

As a result, it is not possible to simultaneously measure both quadratures with arbitrary precision. For any optical field, the quadratures are subject to an uncertainty principle given by

\[ V(\hat{X})V(\hat{Y}) \geq \frac{1}{4} \langle [\hat{X}, \hat{Y}] \rangle^2 = 1 \].

(30)

Within the Wigner phase space representation, this enforces a minimum area for the fluctuations of any optical field [47]. This places a fundamental constraint on measurements of both the amplitude and phase of the field.

3.6.2. Ball and stick diagrams

Wigner distributions of an optical state may be represented qualitatively on a ball and stick diagram, such as those shown in Fig. 4. Diagrams of this kind illustrate in a clear way the consequences of quantum noise on optical measurements. This is particularly true for Gaussian states that are displaced far from the origin (see Fig. 4c, e and f), such as the coherent and squeezed states to be discussed in Sections 4.2 and 4.3, where the extent of the noise balls graphically illustrates the precision constraints quantum noise introduces to both amplitude and phase measurements.

4. Quantum treatment of optical phase measurement

In this section we introduce the quantum Fisher information, which allows a full quantum treatment of the precision achievable in general measurements. Its use is illustrated for the phase estimation experiment considered
Figure 4: Phase space representations of some important quantum states of light. Dashed-lines illustrate the characteristic phase uncertainty of state. a) Fock state (Note: Wigner-negativity associated with Fock states is not depicted), b) vacuum state, c) coherent state, d) squeezed vacuum state, e) amplitude squeezed state, f) phase squeezed state.
in Section 2. Sections 4.3 and 4.4 extend the treatment to squeezed states and NOON states, which are quantum correlated states that are regularly applied in the context of quantum metrology.

4.1. Quantum Fisher Information

One of the key goals of quantum metrology is to study the fundamental limits to precision. The optimal precision achievable with any measurement is quantified by the Cramer-Rao Bound, which states that the Fisher information $F$ limits the precision with which a general parameter $\phi$ may be determined,

$$\Delta \phi \geq \frac{1}{\sqrt{F}}.$$  \hfill (31)

For a classical measurement system, the Fisher information is defined by the probability distribution of measurement outcomes. As discussed in the previous section, however, both quantum states and the quantum measurement process are fundamentally different than their classical counterparts. For quantum measurement processes, the quantum Fisher information is determined by the quantum state of the probe. For any quantum measurement procedure, an input probe state $|\Psi\rangle$ interacts with the system of interest. The quantum Fisher information $F$ quantifies the information contained within the final state $|\Psi_\phi\rangle$ about the parameter $\phi$ (see Fig. 5) and is defined for pure states as \[52\]

$$F = 4 \left( \langle \Psi' | \Psi'_\phi \rangle - | \langle \Psi'_\phi | \Psi_\phi \rangle |^2 \right),$$  \hfill (32)

where primes denote derivatives with respect to $\phi$. The achievable precision improves when a small change in $\phi$ induces a large change in the final state, as this maximizes the first term $\langle \Psi'_\phi | \Psi'_\phi \rangle$. The second term can be understood by considering a first order Taylor expansion of the final state,

$$|\Psi_{\phi+\delta\phi}\rangle = |\Psi_\phi\rangle + \delta\phi |\Psi'_\phi\rangle.$$  \hfill (33)

Figure 5: A quantum treatment of a general measurement process.
with the small perturbation $\delta \phi$ estimated via measurement of the occupation of the state $|\Psi'_\phi\rangle$. The precision of this estimation is limited by $\langle \Psi'_\phi | \Psi_\phi \rangle$, which defines the overlap of the state $|\Psi'_\phi\rangle$ with the unperturbed state and therefore establishes a noisy background to the measurement.

In the specific case of phase measurement, a phase shift $\phi$ within the signal arm of the interferometer is generated by the unitary operator

$$U_\phi = e^{i\hat{n}_{\text{sig}}},$$

where $\hat{n}_{\text{sig}}$ is the photon number operator for the field in the signal arm. This transforms an arbitrary probe state to

$$|\Psi_\phi\rangle = U_\phi |\Psi\rangle.$$

To evaluate the quantum Fisher information, we first note that

$$|\Psi'_\phi\rangle = \frac{d}{d\phi} (U_\phi |\Psi\rangle) = i\hat{n}_{\text{sig}} U_\phi |\Psi\rangle = i\hat{n}_{\text{sig}} |\Psi_\phi\rangle.$$ (36)

Using this relation, it is evident that

$$\langle \Psi'_\phi | \Psi'_\phi \rangle = \langle \Psi_\phi | \hat{n}_{\text{sig}}^2 | \Psi_\phi \rangle = \langle \hat{n}_{\text{sig}}^2 \rangle,$$ (37)

and

$$\langle \Psi'_\phi | \Psi_\phi \rangle = -i \langle \Psi_\phi | \hat{n}_{\text{sig}} | \Psi_\phi \rangle = -i \langle \hat{n}_{\text{sig}} \rangle,$$ (38)

and the quantum Fisher information is therefore given by

$$F = 4 \left( \langle \hat{n}_{\text{sig}}^2 \rangle - |\langle \hat{n}_{\text{sig}} \rangle|^2 \right) = 4 V(\hat{n}_{\text{sig}}).$$ (39)

Since the photon number is conserved by the phase shift operator $U_\phi$, the Fisher information can be evaluated either for the input state $|\Psi\rangle$ or the final state $|\Psi_\phi\rangle$. This very elegant result shows that, fundamentally, the sensitivity of phase measurement on a pure quantum state is dictated solely by the photon number variance of the state in the signal arm of the interferometer. Of course, technical limitations can also limit the sensitivity. Most significantly, the Cramer-Rao Bound may only be reached through an optimal measurement on the optical field, and this measurement may prove intractable, for example requiring perfect photon number resolving detectors.

4.2. Phase sensing with coherent states

We begin our quantum treatment of phase sensing by considering interferometry with coherent states.
4.2.1. Coherent states

Coherent states were introduced to the field of quantum optics in 1963 simultaneously by Sudarshan [46] and Glauber [45, 47, 53], who were motivated by the goal to provide an accurate quantum mechanical description of the field emitted by a laser. Coherent states are eigenstates of the annihilation operator

\[ \hat{a}|\alpha\rangle = \alpha|\alpha\rangle, \]  

(40)

where \( \alpha \) is the coherent amplitude of the state, given by a complex number. As can be easily shown from Eq. (40), the coherent amplitude is related to the mean photon number in the field by

\[ \langle \hat{n} \rangle = |\alpha|^2. \]  

(41)

Of all quantum states, coherent states most closely resemble semi-classical fields such as those considered in Section 2. For instance, photon detection on coherent states exhibits the Poisson distribution expected of random arrivals of uncorrelated photons or random production of photoelectrons. This can be seen by expanding the state in the Fock basis

\[ |\alpha\rangle = e^{-|\alpha|^2/2} \sum_{N=0}^{\infty} \frac{\alpha^N}{\sqrt{N!}} |N\rangle, \]  

(42)

where \( |N\rangle \) is a Fock state consisting of exactly \( N \) photons. The photon number distribution \( P(N) \) is then given by

\[ P(N) = |\langle N|\alpha\rangle|^2 \]  

(43)

\[ = e^{-|\alpha|^2} \sum_{j=0}^{\infty} \frac{|\alpha|^{2j}}{j!} |\langle N|j\rangle|^2 \]  

(44)

\[ = e^{-\langle \hat{n} \rangle} \frac{(\langle \hat{n} \rangle)^N}{N!}, \]  

(45)

where in the last step, we have used Eq. (41) and the orthogonality of the Fock states \( \langle N|j\rangle = \delta_{Nj} \). This is the usual form of a Poisson distribution, with variance

\[ V(\hat{n}) = \langle \alpha|\hat{n}^2|\alpha\rangle - \langle \alpha|\hat{n}|\alpha\rangle^2 = \langle \hat{n} \rangle. \]  

(46)

Eqs. (41) and (46) allow the second order coherence function of a coherent state to be determined from Eq. (20), with the result that \( g_{11}^{(2)} = 1 \). This
indicates that coherent states exhibit no pair-wise correlations between photons, and indeed their pair-wise statistics may be fully understood within a classical framework.

The variances of the amplitude and phase quadratures of a coherent state are

\[
V(\hat{X}) = \langle \alpha | \hat{X}^2 | \alpha \rangle - \langle \alpha | \hat{X} | \alpha \rangle^2 = \langle \alpha | (\hat{a}^\dagger + \hat{a})^2 | \alpha \rangle - \langle \alpha | \hat{a}^\dagger + \hat{a} | \alpha \rangle^2 = 1 \quad (47)
\]

\[
V(\hat{Y}) = \langle \alpha | \hat{Y}^2 | \alpha \rangle - \langle \alpha | \hat{Y} | \alpha \rangle^2 = -\langle \alpha | (\hat{a}^\dagger - \hat{a})^2 | \alpha \rangle + \langle \alpha | \hat{a}^\dagger - \hat{a} | \alpha \rangle^2 = 1 \quad (48)
\]

where we have used the boson commutation relation (Eq. (19)), and the definitions of the quadrature operators (Eqs. (27,28)). We see that the coherent state is a minimum uncertainty state, whose quadrature variances are equal and saturate the uncertainty principle (Eq. (30)). As discussed earlier in Section 3, coherent states provide the minimum uncertainty possible without quantum correlations, and therefore establish an important lower bound on measurement precision. Indeed, a coherent state can be thought of as a perfectly noiseless classical field with additional Gaussian noise introduced with the statistics of vacuum noise. For this reason they are often referred to as “classical light” [2, 35, 16], with the standard quantum limit described as the best precision which can be achieved classically [55, 56], even though truly classical light could in principle be entirely noise free.

4.2.2. Cramer-Rao Bound on phase sensing with coherent states

From Eqs. (31), (39), and (46) it is possible to immediately determine the Cramer-Rao Bound for phase sensing with coherent states which, unsurprisingly, reproduces the semi-classical result given in Eq. (9) and can be reached using the same linear estimation strategy given in Eq. (5) (see Section 2).

It is important to note that the Cramer-Rao Bound as derived here establishes the fundamental limit to the precision achievable for a given photon number at the phase-shifting sample. However, to achieve this bound generally requires additional photons to be introduced within the measurement device. If the total power is constrained, these additional photons must be included in the derivation of the quantum Fisher information.

4.3. Phase sensing with squeezed states

The field of quantum metrology broadly began when Caves showed theoretically that squeezed states of light could be used to suppress quantum noise in an interferometric phase measurement [1]. This principle is currently
used in gravitational wave observatories, with squeezed vacuum used to enhance precision beyond the limits of classical technology [11, 12]. In this sub-Section we introduce the concept of phase sensing with squeezed states.

4.3.1. Squeezed states

The uncertainty principle places a fundamental constraint on the product of amplitude and phase quadrature variances of an optical field (see Eq. (30)). Coherent states spread this uncertainty equally across both quadratures; as their name suggests, squeezed states trade-off reduced uncertainty in one quadrature with increased uncertainty in the other. This is an important capability in quantum metrology, and can be applied to enhance the precision of a broad range of optical measurements. If the amplitude is squeezed as illustrated in Fig 4e), for instance, the photons tend to arrive more evenly spaced than in a coherent field, which is a classically forbidden phenomena known as photon anti-bunching (see Section 3.4). This can be used to reduce the variance in amplitude or intensity measurements, and thus enable precision better than that possible with coherent states. Alternatively, as illustrated in Fig. 4f), the precision of phase sensing can be improved by orientating the squeezed quadrature to be orthogonal to the coherent amplitude of the field.

Figure 6: A Mach-Zehnder phase sensing experiment enhanced via the injection of a squeezed vacuum. The squeezed vacuum entangles the fields within the interferometer, and can be used to suppress quantum noise.
4.3.2. Mean photon number and photon number variance

The mean photon number in a squeezed state is given by

\[ \langle \hat{n} \rangle = \langle \hat{a}^\dagger \hat{a} \rangle = \frac{1}{4} \left( \langle \hat{X}^2 \rangle + \langle \hat{Y}^2 \rangle + i \langle \hat{X} \hat{Y} - \hat{Y} \hat{X} \rangle \right) \]

\[ = |\alpha|^2 + \frac{1}{4} \left( V(\hat{Y}) + V(\hat{X}) - 2 \right), \tag{49} \]

where we have used the definitions of \( \hat{X} \) and \( \hat{Y} \) in Eqs. (27) and (28), and the commutation relation between them (Eq. (29)). We see that unlike the coherent state, squeezed states have non-zero photon number even when their coherent amplitude \( \alpha \) is zero (see Fig. 4d)). While we do not derive it here, in general, the photon number variance of a squeezed state is given by

\[ V(\hat{n}) = |\alpha|^2 \left[ V(\hat{X}) \cos^2 \theta + V(\hat{Y}) \sin^2 \theta \right] + \frac{1}{8} \left[ V(\hat{Y})^2 + V(\hat{X})^2 - 2 \right], \tag{50} \]

where \( \theta \) is the angle between the squeezed quadrature of the state and its coherent amplitude.

4.3.3. Cramer-Rao Bound for squeezed vacuum

As shown in Section 4.1, to maximise the precision of a phase measurement the photon number variance should be made as large as possible. Without loss of generality, we consider the \( \hat{X} \) quadrature to be squeezed, with the \( \hat{Y} \) quadrature maximally anti-squeezed. For fixed photon number \( \langle \hat{n}_{\text{sig}} \rangle \), it can be shown that the maximum photon number variance is achieved when \( \alpha = 0 \). From Eq. (49) we then find that

\[ V(\hat{X})_{\text{opt}} = 2\langle \hat{n}_{\text{sig}} \rangle + 1 + 2 \sqrt{\langle \hat{n}_{\text{sig}} \rangle^2 + \langle \hat{n}_{\text{sig}} \rangle}, \tag{51a} \]

\[ V(\hat{Y})_{\text{opt}} = 2\langle \hat{n}_{\text{sig}} \rangle + 1 + 2 \sqrt{\langle \hat{n}_{\text{sig}} \rangle^2 + \langle \hat{n}_{\text{sig}} \rangle}, \tag{51b} \]

where we have used the relation \( V(\hat{X})V(\hat{Y}) = 1 \) which is valid for pure squeezed states. Substituting these expressions into Eq. (50) and simplifying we find that

\[ V(\hat{n}) = 2 \left( \langle \hat{n}_{\text{sig}} \rangle^2 + \langle \hat{n}_{\text{sig}} \rangle \right). \tag{52} \]
Substitution into Eq. (39) for the quantum Fisher information then yields

$$F_{\langle \hat{n} \rangle \gg 1} = 8 \left( \langle \hat{n}_{\text{sig}} \rangle^2 + \langle \hat{n}_{\text{sig}} \rangle \right),$$

with the Cramer-Rao Bound (Eq (31)) on phase sensing with squeezed light given by

$$\Delta \phi_{\text{squeezed}} \geq \frac{1}{2\sqrt{2}} \left[ \frac{1}{\langle \hat{n}_{\text{sig}} \rangle^2 + \langle \hat{n}_{\text{sig}} \rangle} \right]^{1/2}.$$  \hspace{1cm} (54)

For large $\langle \hat{n}_{\text{sig}} \rangle$ this has Heisenberg scaling ($\Delta \phi \propto \langle \hat{n}_{\text{sig}} \rangle^{-1}$) as has been shown previously in Ref. [57]. Furthermore, Ref. [58] shows that of all possible choices of input state, squeezed vacuum achieves the optimal sensitivity. It should be emphasized, however, that proposals to reach the bound given in Eq. (54) require perfectly efficient photon-number resolving detectors and nonlinear estimation processes, and are not achievable with existing technology [57]. Technical considerations of the effect of inefficiencies are discussed in Section 4.5.

### 4.3.4. Cramer-Rao Bound in the large coherent amplitude limit

In general, increasing levels of quantum correlation are required to achieve a large photon number variance in a pure un-displaced ($\alpha = 0$) quantum state. As a result such states quickly become fragile to the presence of loss, which removes photons and therefore degrades the correlations (see Section 4.5). As a result, most state-of-the-art measurements rely on coherent states with large coherent amplitudes rather than non-classical states. However, with squeezed states it is possible to benefit from both large coherent amplitude and quantum correlations. Considering the limit $|\alpha|^2 \gg \{V(\hat{X}),V(\hat{Y})\}$, Eqs. (49) and (50) become

$$\langle \hat{n}_{\text{sig}} \rangle = |\alpha|^2,$$ \hspace{1cm} (55)

$$V(\hat{n}) = |\alpha|^2 \left[ V(\hat{X}) \cos^2 \theta + V(\hat{Y}) \sin^2 \theta \right].$$ \hspace{1cm} (56)

The quantum Fisher information (Eq. (32)) is then given by

$$F_{|\alpha|^2 \gg \{V(\hat{X}),V(\hat{Y})\}} = 4 \langle \hat{n}_{\text{sig}} \rangle \left[ V(\hat{X}) \cos^2 \theta + V(\hat{Y}) \sin^2 \theta \right].$$ \hspace{1cm} (57)

The optimal phase precision is clearly achieved when the antisqueezed quadrature $\hat{Y}$ is aligned in phase space with the coherent amplitude $\alpha$ of the state (i.e. $\theta = 0$), such that the phase variance is minimized while the amplitude
variance is maximized. In this limit the achievable phase precision is given by

\[
\Delta \phi_{\text{squeezed}} \geq \frac{1}{2 \sqrt{\langle \hat{n}_{\text{sig}} \rangle V(\hat{Y})}} = \sqrt{V(\hat{X})} \Delta \phi_{\text{SQL}}
\]  

(58)

where the relevant standard quantum limit for phase measurement \( \Delta \phi_{\text{SQL}} \) is given in Eq. (9). Since \( V(\hat{X}) < 1 \), we see that squeezed light allows precision beyond the standard quantum limit. Similarly to the case of phase sensing with coherent states, this limit may be reached using a straight-forward linear estimation strategy.

The expressions in Eqs. (55) and (56) allow us to calculate the second order coherence function for bright squeezed states, as described in Eq. (20). This shows that

\[
g_{11}^{(2)} = 1 + |\alpha|^2 \left( V(\hat{X}) \cos^2 \theta + V(\hat{Y}) \sin^2 \theta - 1 \right).
\]  

(59)

We can thus see that phase squeezed light with \( \theta = 0 \) is bunched \( (g_{11}^{(2)} > 1) \); by contrast, amplitude squeezed light with \( \theta = \pi/2 \) is anti-bunched \( (g_{11}^{(2)} < 1) \), which is one clear indicator of quantum correlations (see Section 3.4).

4.3.5. Interferometry combining squeezed vacuum with a coherent field

The scenario described in Eq. (58) corresponds to a single bright squeezed state propagating through a phase shifting element. Most experimental demonstrations apply an alternative approach, in which a squeezed vacuum and coherent state are combined on a beamsplitter and then propagate through an interferometer (see Fig. 6). The resulting two fields in the interferometer are an entangled pair of bright squeezed states, with anticorrelated quantum fluctuations. The phase of the input fields is chosen to align the coherent input to the antisqueezed quadrature, which maximizes the quantum Fisher information for a differential phase shift measurement. A full analysis of this approach shows that the phase precision can be enhanced by \( \sqrt{V(\hat{X})} \), similar to Eq. (58) [1].

This is the basic approach considered by Caves in the first quantum metrology proposal [1], and which is now used in gravitational wave observatories [11, 12]. It is particularly useful since the quantum state preparation can be separated from the generation of a large coherent amplitude, allowing both states to be independently optimized. Within this framework, the non-classical state provides a fixed enhancement in precision for the arbitrarily
bright coherent state. It is of note that for constrained photon occupation in
the non-classical state, of all possible choices of input state squeezed vacuum
provides the largest possible precision enhancement to the bright interfero-
metric phase measurement [58].

4.3.6. Generation of squeezed states

Squeezed states of light are produced via nonlinear optical interactions.
The essential feature of such nonlinear interactions is a reversible phase sen-
sitive amplification of the optical field, such that the fluctuations of one
quadrature are noiselessly amplified while the fluctuations of the orthogonal
quadrature are noiselessly de-amplified. Phase sensitive amplification can be
achieved using a wide range of nonlinear processes, such as optical parametric
oscillation and amplification [59, 36], optical Kerr nonlinearities [60], second
harmonic generation [61], and four-wave mixing in an atomic vapour [62, 63];
and each of these approaches has been used to generate squeezed light. To
take one example, amplitude squeezed light can be generated via second har-
monic generation, where two photons combine to produce a single frequency-
doubled photon with a probability proportional to the square of the ampli-
tude of the incident field. The quantum fluctuations in the amplitude of
the field then translate to fluctuations in the probability of second harmonic
generation. Thus, when the field amplitude fluctuates toward a larger value,
the second harmonic generation becomes more efficient and more of the light
is lost. A fluctuation of field amplitude toward a smaller value will result
in less efficient second harmonic generation, and consequently smaller loss.
The net effect is to suppress the amplitude fluctuations, which can result in
fluctuations below the vacuum level, with a consequent increase in the phase
fluctuations.

Much of the effort in the development of squeezed light sources over the
past decade has focussed on achieving sources useful to enhance measure-
ments in gravitational wave observatories [3]. One important requirement
for this application is a high degree of squeezing which can allow an ap-
preciable enhancement in precision. In absolute terms, the strongest single-
mode squeezing is currently achieved in optical parametric oscillators that are
pumped with light at 532 nm or 430 nm and which produce vacuum squeezed
fields at 1064 nm [64, 59, 36] and 860 nm [65], respectively. Such sources are
capable of squeezed quadrature variances as small as $V(\hat{X}) = 0.054$ [64]. A
second key requirement is for the squeezed light source to allow quantum
enhanced precision at low frequencies [66, 67, 68]. Squeezed light has a fi-
nite frequency band of enhancement, and many sources only provide squeezing in the MHz regime [16, 69]. This is inadequate for gravitational wave detection, where most of the signals are expected at Hertz and kilohertz frequencies [3]. This frequency band is also important to biological experiments, as it encompasses most biophysical dynamics studied to date (see Section 6.3). Consequently, biological quantum metrology could directly benefit from the advances toward gravitational wave detection. Squeezed light has now been demonstrated at frequencies as low as 1 Hz [70], though light which is squeezed to 10 Hz is still considered state-of-the-art [12, 36].

In a typical squeezed light source, the nonlinear medium is placed within an optical resonator to increase the strength of the nonlinear interaction and thus the magnitude of the squeezing. This generally allows only a single mode of the optical field to be squeezed, as is required to enhance single-parameter measurements such as phase or intensity measurements. However, efforts have also been made to generate strong multimode squeezing for applications such as quantum enhanced imaging (see Section 5). In particular, multimode degenerate optical resonators have been developed to allow resonant enhancement of as many as eight modes [71]; while the strong optical nonlinearity near the optical resonances of an atomic vapour allows strong squeezing without use of an optical cavity, allowing generation of a multimode squeezed vacuum state over hundreds of orthogonal spatial modes [62, 63]. Another source of highly multimode quantum correlated light is parametric down-conversion, which produces a photon pair from a single high-energy photon. To conserve momentum, the photons always propagate with opposing directions, such that they occupy coupled spatial modes.

4.4. Phase sensing with NOON states

As discussed in Section 4.1, the achievable phase precision improves as the photon number variance increases (see Eq. (4.1)). In the limit that exactly $N$ photons are used, the precision is maximized for a NOON state, in which the constituent photons are in a superposition of all occupying either the signal or reference arm of the interferometer, with the other unoccupied [55]. In the number state basis, the NOON state can be represented as

$$|\Psi_{\text{NOON}}\rangle = \frac{1}{\sqrt{2}} (|N\rangle_{\text{sig}}|0\rangle_{\text{ref}} + |0\rangle_{\text{sig}}|N\rangle_{\text{ref}})$$ (60)
When using a NOON state, the quantum Fisher information for phase estimation (Eq. (39)) is determined by

\[
\langle \Psi_{\text{NOON}} | \hat{n}_{\text{sig}} | \Psi_{\text{NOON}} \rangle = \frac{1}{\sqrt{2}} \langle \Psi_{\text{NOON}} | N \rangle_{\text{sig}} | 0 \rangle_{\text{ref}} - \frac{1}{\sqrt{2}} \langle \Psi_{\text{NOON}} | \hat{n}_{\text{sig}} | 0 \rangle_{\text{sig}} | N \rangle_{\text{ref}} \]

\[= N \langle \Psi_{\text{NOON}} | N \rangle_{\text{sig}} | 0 \rangle_{\text{ref}} \]

\[= \frac{N}{2} \] (62)

\[
\langle \Psi_{\text{NOON}} | \hat{n}_{\text{sig}}^2 | \Psi_{\text{NOON}} \rangle = \frac{1}{\sqrt{2}} \langle \Psi_{\text{NOON}} | \hat{n}_{\text{sig}}^2 | N \rangle_{\text{sig}} | 0 \rangle_{\text{ref}} + \frac{1}{\sqrt{2}} \langle \Psi_{\text{NOON}} | \hat{n}_{\text{sig}}^2 | 0 \rangle_{\text{sig}} | N \rangle_{\text{ref}} \]

\[= \frac{N^2}{\sqrt{2}} \langle \Psi_{\text{NOON}} | N \rangle_{\text{sig}} | 0 \rangle_{\text{ref}} \]

\[= \frac{N^2}{2} \], (65)

such that

\[
\mathcal{F} = 4 \left( \langle \Psi_{\text{NOON}} | \hat{n}_{\text{sig}}^2 | \Psi_{\text{NOON}} \rangle - | \langle \Psi_{\text{NOON}} | \hat{n}_{\text{sig}} | \Psi_{\text{NOON}} \rangle |^2 \right) = N^2 \] (67)

and

\[
\Delta \phi = \frac{1}{N}. \] (68)

As described earlier in Eq. (10), this corresponds to the Heisenberg limit on phase estimation. It has been shown that the NOON state is optimal for states which contain exactly \( N \) photons; although in principle states with indeterminate photon number such as the squeezed vacuum have been shown to allow slightly superior performance \[72, 73, 74, 75\] (See Section 4.3).

To understand why NOON states allow enhanced precision, it can also be instructive to consider the evolution of the state through the interferometer. When a phase shifting operator \( e^{i \phi \hat{n}} \) is applied to a number state, it evolves as

\[
e^{i \phi \hat{n}} | N \rangle = \sum_{j=0}^{\infty} \frac{(i \phi)^j}{j!} | N \rangle = e^{i \phi N} | N \rangle. \] (69)

Consequently, the phase shifting operator applies a phase shift of \( N \phi \) to a number state. NOON states acquire this amplified phase shift. By contrast, using the Fock state expansion of coherent states given in Eq. (42), we see
that a coherent state $|\alpha\rangle$ evolves as

$$
e^{i\phi\hat{n}}|\alpha\rangle = e^{i\phi} e^{-|\alpha|^2/2} \sum_{j=0}^{\infty} \frac{\alpha^j}{\sqrt{j!}} |j\rangle = e^{-|\alpha|^2/2} \sum_{j=0}^{\infty} \frac{(e^{i\phi}\alpha)^j}{\sqrt{j!}} |j\rangle = |e^{i\phi}\alpha\rangle,
$$

which corresponds to the same phase shift $\phi$ for any mean photon number. The enhanced phase precision achievable with a NOON state originates with this amplification of the relative phase shift [55]. This is evident in the read-out; an interferometer using coherent light will show one full oscillation in the detection statistics over a $2\pi$ phase shift, whereas an $N$ photon NOON state exhibits $N$ full oscillations. This is fundamentally interesting because it is a purely quantum effect which could not follow from a classical wave treatment. The decreased spacing between interference fringes is sometimes referred to as super-resolution, which can cause significant confusion to those outside the field of quantum metrology. Classically, the term super-resolution denotes technologies which allow the diffraction limit on imaging resolution to be overcome (see Section 7). While imaging resolution is closely related to the interference fringe spacing, and NOON states can in principle allow improved resolution in imaging (see Section 5.4), the interference fringe spacing has little practical relevance in an interferometric phase measurement. For phase sensing applications, the advantage of NOON states is that they can provide enhanced precision, often referred to as super-sensitivity.

### 4.4.1. Generation of NOON states

A single photon NOON state can be generated by splitting a single photon on a beam splitter, which places the photon into a superposition of reflecting and transmitting. However, the Heisenberg limit coincides with the standard quantum limit for $N = 1$, so this cannot be used to enhance precision. Most sensing applications instead apply two photon NOON states, which are produced from entangled photon pairs via two-photon interference in a Hong-Ou-Mandel (HOM) interferometer [44] (see Fig. 2). A nonlinear crystal is pumped at double the optical frequency to produce the entangled photons pairs, which are then collected and passed through the interferometer. Provided neither photon is lost, this deterministically combines the pair of photons together in one of the interferometer outputs. When used for phase sensing, this can provide a factor of $2^{1/2}$ enhancement in precision (or 3 dB in power).

While a NOON state with higher photon number should allow improved precision, currently these cannot be generated deterministically. Such states
can only be generated with low probability from higher order nonlinearities, such as two pump photons annihilating into four entangled photons. The largest NOON state generated to date contained 5 photons, with an average photon flux below 1 s$^{-1}$ \cite{38}. At such low flux the absolute precision achievable with such states is far inferior to routine measurements with modest power coherent states. Furthermore, the NOON states produced in Ref. \cite{38} co-propagated with well over 1000 s$^{-1}$ photons in other states. Consequently, post-selection was required to suppress unwanted detection events. Since post-selection is not necessary with coherent optical fields, this artificially improves the precision comparison \cite{76}.

The low photon numbers in photonic NOON states also constrains the maximum enhancement which is achievable, such that even a perfect measurement using 5-photon NOON states is limited to 7 dB of quantum enhancement, with real experiments achieving far less. By comparison, 12.7 dB of enhancement has been experimentally observed using squeezed light \cite{64}.

4.5. The effects of optical inefficiencies

As discussed in Section 4.1, the Cramer-Rao bound is only achievable with a perfect measurement. To predict the achievable precision in a real experiment, it is important to consider the effects of imperfections and inefficiencies.

A number of inefficiencies can collectively be considered as optical loss. Inefficient detection, for instance, is equivalent to attenuation of the light followed by perfect detection. All optical loss can be modeled as a beam splitter which couples the mode of interest to an unknown environment. This discards some of the light, while the unused input adds vacuum fluctuations to the detected field (see Fig. 4b). Since the coherent state is equivalent to displaced vacuum fluctuations, the noise properties of a coherent state are preserved by loss. This is not true in general, and the non-classical statistics of quantum correlated states are degraded by loss. Although all states are degraded by loss, the degradation is particularly severe for a NOON state, since loss of a single photon deterministically localizes the remaining light into one arm of the interferometer and completely erases any entanglement \cite{55}. In the limit of large photon number and non-negligible loss, the loss of one or more photons is almost guaranteed and the NOON state becomes unusable. In this limit, it has been shown that optimal precision is provided by a squeezed state with a large coherent amplitude \cite{77}. Below this asymptotic limit, however, more complex states are optimal; see Refs. \cite{41, 78, 79}. 

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5. Quantum enhanced imaging

The discussion above describes the influence of quantum noise in the estimation of a single parameter. Additional complexities arise in imaging, which is broadly defined as a measurement in which spatial variations in a parameter are mapped out. For instance, the images formed in a camera or eye are constructed by mapping the incident light intensity over a range of incident angles. Such optical imaging devices achieve spatial resolution by simultaneously sensing the light at different locations. This parallel imaging approach requires multiple sensors which can independently and simultaneously sense localized properties in a sample. One can also form an image by scanning a sensor over the area of interest, and sequentially building up the spatial profile. This approach is taken in atomic force microscopy (AFM), for instance. Scanned imaging only requires a single sensor, but can only form a reliable image of a sample if both the imaging equipment and sample are static over the scanning time. In many cases, this makes scanning measurements poorly suited to imaging of sample dynamics, and also very susceptible to equipment instability. However, this can be avoided with extremely fast scanning, with a recently developed scan-based technology capturing optical images at a rate far faster than a high-speed multi-pixel camera [80].

The quality of any image is determined by its contrast and resolution. Contrast is closely related to precision, and describes the amplitude of the observable spatial features relative to the measurement uncertainty. Resolution describes the smallest length scale over which a change can reliably be sensed. In optical imaging, the resolution is often fundamentally constrained by the wavelength of the light used, as discussed below in Section 5.2.

5.1. Spatial mode decomposition

As with other optical measurements, quantum correlations can allow imaging sensitivity to surpass the standard quantum limit. To extend the analysis of Section 4 to imaging, it is important to consider the spatial modes included in the measurement. Optical imaging applications typically sample the entire field of view simultaneously with a multipixel detector. The detected optical field can always be decomposed into an orthogonal set of modes, with the full number of orthogonal sampled modes given by the number of spatially resolvable points within the field of view, limited either by the diffraction limit or the number of pixels in the detector. As discussed in
Section 3.1, the total optical field can be analyzed by treating each spatial mode independently.

If non-classical states are introduced to enhance precision, it is important to note that the enhancement is only present in the spatial modes that exhibit quantum correlations. Measurements of all orthogonal modes remain bounded by the standard quantum limit. It is also important to note that the spatial mode of the probe light need not correspond to the measurement mode; for instance, deflection of a laser beam with Gaussian profile couples some of the incident light from the TEM00 mode to the TEM01 mode. As such, a deflection measurement is not enhanced by introducing quantum correlations to the laser beam mode, but instead the correlations must be present in the orthogonal TEM01 mode [81].

A typical imaging application might sample thousands of spatial modes. It is therefore beneficial to establish quantum correlations across many spatial modes. However, the most powerful squeezed light sources are based on optical cavities which confine all the generated correlations to a single mode. It is possible to utilize multiple single-mode squeezed light sources to produce multi-mode enhancement, though this approach is not scalable to a large numbers of modes. To date, this has only been demonstrated with a maximum of eight spatial modes [71], and such sources have not yet been applied in multimode imaging. They have, however, recently been applied to scanning probe-based imaging which only required single-mode measurement [17].

As discussed above, few-mode squeezed light sources are not well suited to multi-mode imaging. By contrast, light sources which produce quantum correlations in a continuum of spatial modes (see Section 4.3) can be used in a wide range of imaging applications. For instance, multimode entangled photon pairs produced via parametric down-conversion have been applied in proof-of-principle demonstrations of sub-shot noise absorption imaging [26], ghost imaging via photon correlations [82], improved image reconstruction against a noisy background [83], and noiseless image amplification [84, 85]. Similarly, multimode squeezed light produced via four-wave mixing in an atomic vapour has been used to generate entangled images [62], and to estimate the shape of an absorbing mask with enhanced precision [86]. However, these approaches are so far limited to the photon counting regime, with low flux limiting their practicality for most applications. Furthermore, such experiments require more elaborate detection strategies to extract the information from the non-classical state, which currently presents a barrier to
Figure 7: (A) When light is focused through a lens, the incident angle $\theta$ determines the focal position $x$ (see Eq. (71)). However, diffraction establishes a minimum area in which a field can be focused. Considered in reverse, this same principle establishes the minimum angular range outside of the lens which a point source at $x$ will emit into. This has the effect of blurring an optical image, with point features broadened by the point-spread function. (B) This blurring limits the resolution with which two point sources can be resolved. In this case, the two individual sources (dashed lines) cannot be resolved from the total detected light (solid line), though its broadened profile allows inference that more than one point source is within the detected bright spot.

their widespread use [87]. Resolution of these technical barriers could enable a wide range of quantum technologies to see practical imaging application, and would signify a crucial advance in quantum imaging.

5.2. Diffraction limit

A number of important quantum imaging technologies aim to overcome the diffraction limit. The diffraction limit (also known as the Rayleigh limit) is an important constraint in optical microscopy, limiting the resolution of any linear far-field optical imaging technique, including absorption imaging, phase contrast microscopy, and differential interference microscopy. This states that the smallest resolvable features must be separated by at least

$$x_{\text{min}} = \frac{\lambda}{2 \text{NA}}, \quad (71)$$

where $\lambda$ is the optical wavelength and NA is the numerical aperture of the imaging lens. This describes the smallest spot to which light can be focused given the NA of the lens system (referred to as the point-spread function), with smaller focal spots prevented by diffraction of the optical waves.
Equivalently, $x_{\text{min}}$ also describes the smallest separation required between point sources to prevent their fields from overlapping upon detection (see Fig. 7). Optical microscopes operating in visible wavelengths are therefore constrained to resolution above approximately 200 nm. As will be discussed later, this is a severe constraint in cellular studies, as few sub-cellular structures are above this resolution limit (see Fig. 8).

If the point-spread function of the imaging objective is precisely known, it is possible to infer details of an optical image with resolution below the diffraction limit (see Fig. 7B). Details which cannot be directly observed in the image can be statistically reconstructed in a process known as image deconvolution [88]. Although this might appear to allow unlimited resolution, in reality the resolution is constrained because the reconstructed image becomes unreliable for particularly small feature sizes [89].

5.2.1. Classical super-resolution techniques

The optical diffraction limit restricts the resolution of any direct far-field optical imaging technique. However, the diffraction limit can be overcome classically in the presence of nonlinearities. Two-photon absorption, for instance, occurs classically at a rate proportional to the square of the intensity (see Section 3.4). This allows the two-photon absorption to be localized with improved resolution. In general, any process which depends on the $N$th power of the optical intensity can be classically resolved with a resolution of $x_{\text{min}}N^{-1/2}$ [90]. This is used to achieve superior resolution in multi-photon microscopy, in which multi-photon absorption processes are driven [91].

In recent years, a wide range of techniques have been developed which utilize the nonlinearities of fluorescent particles to achieve super-resolution. A number of particularly powerful techniques were developed for photo-switchable fluorescent probes, including stimulated emission depletion (STED) microscopy [92, 93], photoactivated localization microscopy (PALM) [94], and stochastic optical reconstruction microscopy (STORM) [95]. These techniques rely on a pump field to populate the particles into a non-fluorescing state, such that the observed fluorescence is localized only in the region where the field is absent. They have enabled great progress in biological research by allowing cellular structure to be characterized at the nanometre level.

In addition to these approaches which use photo-switchable probes, a number of super-resolution techniques rely on saturation. When imaging a saturable absorber, the absorption can scale with extreme nonlinearity near the saturation threshold. Since this can access extremely high order nonlin-
earities, it can allow extremely narrow resolution. This principle has enabled
the recent development of saturated structured illumination microscopy, with
fluorescent particles pumped into the saturation regime to allow resolution
smaller than 50 nm [96]. Saturation in non-fluorescent materials can also
be used to achieve super-resolution. Recently, a photoacoustic microscopy
experiment achieved resolution of less than half the diffraction limit when
imaging gold nanoparticles [97].

Even in the absence of nonlinearities, the diffraction limit can be bro-
ken. The field leaving the microscope objective is closely approximated as
the spatial Fourier transform of the field at the focus. The diffraction limit
can be considered a natural consequence of the objective aperture, as it
prevents measurements of high spatial frequencies. With structured illumi-
nation, however, the spatial frequencies at the focus can be modulated, which
shifts some high frequency information to frequencies below the diffraction
limit and thus allows the resolution to be halved [98].

5.3. Super-resolution in ghost imaging

Ghost imaging is one prominent quantum imaging technique which al-
lows an apparent violation of the diffraction limit described in Eq. (71). In
its original configuration, ghost imaging relied upon entangled photon pairs
produced via parametric down-conversion [82]. Since the down-conversion
process conserves momentum, the propagation direction of the two photons
are highly correlated. The photons are focused with a lens, with one arm
imaged onto a camera while the other is imaged onto an absorbing sample.
Since the focus positions are highly correlated, the camera provides informa-
tion about the position at which the probe photon reached the sample. A
simple transmission measurement then allows reconstruction of an image.

Initially, ghost imaging was seen as a purely quantum imaging proto-
col [82]. However, later experiments demonstrated similar ghost imaging with
classical photon correlations in the form of pseudorandom laser speckle [99].
This led to a lively debate regarding which aspects were truly quantum [100],
with the eventual conclusion that thermal light could reproduce nearly all
features of ghost imaging with entangled photons, but with degraded con-
trast [100, 101].

For the ghost imaging scheme described above, the focusing lens limits
the achievable resolution. However, similar imaging procedures can also be
performed without a focusing lens. This approach can be understood easi-
est within context of classical ghost imaging, with the achievable resolution
limited by the minimum size of the laser speckle \[99\]. This therefore provides resolution which is independent of the \(NA\) of the lens used to image the field onto a detector, such that the resolution can appear to break the diffraction limit of Eq. (71). Since the positions of speckle foci are randomly modulated, this imaging technique effectively performs a raster scan through 3D space. The sequential nature of this imaging procedure also allows it to violate of the Fourier limit, which imposes a trade-off between the resolution of simultaneous images at near-field and far-field \[99\]. It does not, however, allow the sub-wavelength resolution which is highly sought after in biological microscopy. In fact, the resolution limit due to speckle is given by approximately \(\lambda z/D\), where \(z\) is the distance from the noisy light source to the image, and \(D\) is its diameter \[99, 100\]. If we consider the light source itself to be an element which focuses light into speckles, its \(NA\) is given approximately as \(2D/z\), and the resolution is constrained by diffraction as described in Eq. (71). Consequently, the diffraction limit is not violated in a treatment of classical ghost imaging which considers the focusing power of both the imaging lens and the light source, while a similar result also holds for ghost imaging with entangled photons \[100\].

5.4. Super-resolution quantum lithography

As discussed above, classical diffraction limits the resolution of far-field optical imaging systems. Non-classical states of light follow classical diffraction and cannot be focused into a smaller spot size than specified in Eq. (71). Consequently, these states do not allow a resolution enhancement in far-field optical imaging with linear measurement. However, quantum correlations in non-classical states can allow distinctly non-classical characteristics in multi-photon or nonlinear measurement schemes, as discussed in Section 3. For instance, although an \(N\) photon NOON state can only be focused into a diffraction-limited region described by \(x_{\text{min}}\), coincident detection of all \(N\) photons can be localized to \(x_{\text{min}}N^{-1}\) \[102\]. Consequently, it is in principle possible to achieve a resolution enhancement of \(N^{-1/2}\) in multi-photon absorption microscopy, or in lithography of a multi-photon absorbing substrate \[73, 102\].

If, however, single photon losses are present, the entanglement of the NOON state is quickly lost. In principle the enhanced resolution could still be observed in the instances that no photons were lost, which can be seen via post-selection of \(N\) photon detection events. However, high losses
and difficulties in finding materials with suitably high multi-photon absorption has posed a severe constraint. Although the narrowed region of multi-photon coincidences was observed with photon-counting detectors in the year 2001 [102], to date no experiment has succeeded in achieving super-resolution on a multi-photon absorber, as required for its application in imaging or lithography [103].

In the above proposal, only the photons which are co-localized are included in the measurement. It has been shown that the centroid of the entangled field can be estimated from measurement of all the photon arrivals, which therefore improves efficiency by a factor of approximately $N$ while maintaining the resolution of $x_{\text{min}} N^{-1}$ [104]. This has recently been demonstrated experimentally [105]. This constitutes a demonstration of quantum imaging below the diffraction limit. However, it is important to note that optical centroid measurement is not a fundamentally diffraction-limited problem. For comparison, the centroid of a coherent field can be estimated to $x_{\text{min}} N^{-1/2}$ [35, 39], and is routinely estimated with precision many orders of magnitude smaller than $x_{\text{min}}$ in applications such as optical tweezers and atomic force microscopy.

6. Challenges for biological measurement

Quantum metrology is relevant to biology because it holds the promise to achieve unprecedented sensitivity. This relevance has been recognized from the earliest stage of quantum enhanced measurements [6, 4, 7, 5, 106]. Importantly, optical measurements of cellular scale biology are always invasive, with light inducing photochemical disruption and damage. This places power constraints on the illuminating light, which sets an upper limit on the classically achievable precision. Improved resolution is also needed, as many sub-cellular features have nanometre scale and only interact weakly with the incident light. Here, the unique challenges and requirements of biological measurement are described.

6.1. Resolution requirements

The overarching goal of biophysical research is to understand the mechanisms by which living organisms function. This encompasses a vast range of different research areas, ranging from studies of the mechanics and utility of single biomolecules, to understanding how cells function collectively.
Figure 8: Length scales in biology. The diffraction limit of visible light restricts far-field imaging resolution to around 200 nm, which is the approximate scale of organelles. Single proteins or other biomolecules are not typically observable with a light microscope, and super-resolution techniques are required to study their function and structure. As discussed in Section 6.3, the size scale is also strongly correlated with the characteristic frequencies of biological dynamics. Larger structures exhibit slower dynamics, with tissue dynamics typically occurring at Hz frequencies, while single-molecule dynamics can reach MHz frequencies. Reprinted by permission from Macmillan Publishers Ltd: Scitable, Ref. [107], Copyright (2010)
as organs (see Fig. 8). When imaging organs, the primary difficulty is often to accurately image through surrounding tissue which obscures the view, while maintaining sufficient resolution to observe features which can be as small as a few cells. While such structures can easily be observed by removing the surrounding tissue, this is a highly destructive process. Imaging techniques which can accurately and non-destructively image through tissue are extremely important for studies of changes and growth within living creatures, and also have important applications in medical diagnosis.

In contrast, studies at the cellular level are typically limited by the small size of the sub-cellular components. A mitochondrion typically has width of around 200 nm, approximately equal to the diffraction limit on resolution in a light microscope. Many other organelles are much smaller, and in almost all cases, none of the individual proteins can be individually resolved (see Fig. 9). Consequently, sub-cellular features cannot be reliably separated with a conventional light microscope, and techniques which can resolve different structures are particularly useful. Huge advances in biophysics have been enabled by nanoscale imaging techniques (see Section 5.2.1), which have allowed direct observation of protein assemblies. Despite this, many biomolecules remain too small to be directly imaged. For instance, nanometre resolution would be required to observe the nucleotides in a DNA molecule. Consequently, such structures are typically studied with methods that do not involve construction of a direct image.

6.2. Sensitivity requirements

While the size scale of biological structures sets natural resolution requirements that are broadly relevant throughout biological imaging, there is no corresponding sensitivity limit which can be commonly applied in biological measurements. A number of applications are currently limited by the achievable sensitivity, such as single-molecule sensing [108, 109] and biological mass measurements [110]. By contrast, the sensitivity requirements of some applications has already been saturated, with accuracy now limited by external factors. For instance, most methods to distinguish healthy and cancerous cells operate with accuracy limited by the cell-to-cell variations rather than instrument sensitivity [80]. Likewise, thermal fluctuations introduce stochastic motion to small particles which can place a precision limit on the characterization of many biomechanical forces [111]. A common approach used to observe the dynamics of small subcellular structures is to attach large marker particles to enhance the interaction with light. Such markers slow
the natural biomolecular mechanics; this approach is somewhat analogous to studying the movement of a runner by attaching a ball-and-chain to them and tracking its motion. Furthermore, a large marker particle is subject to a large stochastic thermal forces, which constrains the achievable force precision. Consequently, these observations can be improved with use of smaller markers or label-free detection [112]. In many cases, however, label-free measurements require precision beyond the limits of existing technology [112]. Consequently, although many existing biomolecular force measurements are currently limited by thermal fluctuations, an improvement in sensitivity is still highly relevant if it could allow smaller markers or label-free detection.

6.3. Typical frequencies of interest

Biological structures can exhibit dynamic behaviour over a wide range of frequencies. While there always exists a wide range of characteristic frequencies, as a general rule larger structures exhibit slower dynamics (see Fig. 8), and active processes such as movement and control occur far faster than other functions such as digestion and growth. At the level of tissues and organs, many active processes occur around the Hz timescale. Examples include the heartbeat of all animals, which range from 0.1 Hz in blue whales to 21 Hz in hummingbirds; which reflects an $M^{-1/4}$ scaling with body mass $M$ [113]. At the cellular scale, many dynamics occur high in the Hz range; for instance, muscle cell contraction occurs at timescales of order 100 Hz, though nerve cells can pass on a neural signal at rates into the kHz [114]. Subcellular dynamics are usually even faster, often occurring at kHz timescales; the molecular motor kinesin takes steps with a characteristic time of 5 ms (200 Hz), while the motor myosin steps with a characteristic time of 660 µs (1.5 kHz) [115]. As studies progress to single molecules, the frequencies can reach MHz; for instance, light detection in a retinal cell is triggered by a conformational change of rhodopsin which occurs over a few tens of nanoseconds [116]. Similarly, protein folding can occur over timescales that range between 50 ns and 10 µs [117].

Although the frequencies described above correspond to the timescales of active biophysical processes, biological measurements can also be relevant over vastly different timescales. Measurements of growth and respiration, for instance, occur on much slower timescales. Likewise, a biological structure can have important mechanical relaxation properties which are only observable at frequencies much higher than any related biophysical process [118]. Although this guide describes the approximate frequency range of interest to
a wide range of biophysical experiments, there are many important biological experiments which fall outside of the described frequency ranges.

6.4. Optical damage in biology

Light which is used to observe a cell can also damage and kill it. Optical destruction of a cell during experiments is sometimes referred to as “optiction”, and is a serious concern in many studies [119, 8]. Even if the cell remains alive, optical damage can permanently disrupt cellular function. Some studies find that cells cannot divide after being studied, even if they are not visually damaged and continue to respire [9]. In addition to damage, incident light can also heavily disrupt cellular function. Altogether, optical damage and biophysical disruptions can complicate efforts to observe the state of a healthy cell, and places stringent constraints on the optical power levels that can be used in biological measurements.

6.4.1. Optical heating

There are two major pathways by which light can disrupt cellular function. Firstly, optical heating increases the temperature, which can cause vast changes to the cellular respiration and division [120, 121]. With sufficient heating, this can destroy the cell. Laser heating also induces thermal gradients, which influences the diffusive transport of nutrients and biomolecules in the cell.

The biophysical effect of optical heating has been shown to vary with the ambient temperature. Although some cellular experiments are performed at room temperature, this significantly reduces the respiration of most cell types, and over an extended period of time can cause permanent damage to some mammalian cells [122]. To avoid this, many cellular experiments use incubators to raise the temperature to a biologically active regime. For experiments operating at incubation temperatures, laser heating resulting from optical tweezers has been found to induce substantial damage within 10 seconds [10]. When operating at room temperature, however, much less laser heating damage is observed even after extended periods of study [10].

Although the cell itself absorbs some of the light, much of the optical heating follows from heating of the water in and around a cell. Consequently, the optical heating rate is approximately proportional to the absorption coefficient of water [120]. This coefficient is strongly wavelength dependent, with relatively high absorption in the infra-red, and low absorption in the visible spectrum (shown in Fig. 9). As such, optical heating is a serious constraint
Figure 9: The optical losses in a biological experiment. These are dominated by the absorption of water (blue line) and dipole scattering loss (dashed red line). Above 500 nm, the absorption spectra of water tends to increase with wavelength, such that optical heating becomes increasingly severe. However, photochemical damage decreases with wavelength. The most common wavelength for squeezed light generation is 1064 nm (Section 4.3), which is also popular for optical tweezers and other applications where damage constrains the usable power since it falls very near a local minima in absorption. While the absorption of water is low in visible wavelengths, dipole scattering loss scales as $\lambda^4$ and can be very large. The total scattering loss depends on the sample, though it is common for optical loss to be minimized in the near infra-red [123]. Water absorption spectral data taken from Refs. [124, 125].
when operating in infra-red, but can be largely neglected when operating in visible wavelengths.

### 6.4.2. Photochemical effects

Although operation at visible wavelengths reduces the potential for photothermal damage, it increases photochemical intrusion upon the cell. One particularly toxic photochemical effect follows when light disassociates molecules and produces reactive oxygen species \[126\]. It is known that the cell division rate is substantially changed by photochemical effects due to illumination \[127\], as is enzyme activity \[128\] and many other processes. When too much light is used these photochemical effects are fatal for the cells \[129\]. The damaging chemical effects are dramatically increased as the wavelength decreases, as this provides more energy to each photon and allows access to a greater range of photochemical pathways \[119\].

Incident light can also induce damage by disrupting the cellular control mechanisms \[10\]. Incident light can induce pore formation in a cell membrane, which is referred to as optoporation. These pores are an important part of a cell's regulatory system, controlling the flow of water and nutrients through the membrane. When they are overstimulated with an optical probe, however, the membrane becomes permeable. Water then flows into the cell to approach equilibrium water concentrations, which pressurizes the cell and can cause it to rupture \[130\].

To minimize such effects, biophysical experiments can be performed with infra-red optical wavelengths. The collective damage of optical heating and photochemical stimulation is minimized in the near infra-red \[121\], \[119\], \[131\]. This wavelength window also corresponds to a broad minima in the absorption of light by biological tissue which is known as the “therapeutic window” \[123\]. Since minimizing the optical loss also minimizes the energy imparted to the biological sample, it might seem unsurprising that damage is reduced as the loss is minimized. However, it should be noted that optical damage and optical loss are not fundamentally related at visible wavelengths, with damage dominated by photochemical effects and optical loss dominated by dipole scattering \[123\]. In biophysical experiments 780 nm or 1064 nm wavelength lasers are often chosen for operation within the therapeutic window, with the additional benefit that low noise lasers are readily available at these wavelengths, and 1064 nm lies close to a local minima in the optical absorption. These wavelengths are similar to those used in squeezed light generation, with the best single-mode squeezed light sources to date oper-
ating at 860 nm or 1064 nm (see Section 4.3). Such sources are therefore already well suited to biophysical studies. However, while minimizing the damage can make the light non-fatal to the cell, it still perturbs a wide range of cell functions which can influence the biological parameter under study.

6.5. Practical considerations

Biological experiments introduce unique challenges which are foreign to typical quantum metrology experiments. While most quantum metrology experiments explore static systems, cells are constantly respiring and growing. This complicates both data analysis and interpretation. Growth and division rates vary wildly with the strain of cells. To take a specific example, consider *Saccharomyces cerevisiae* yeast cells, which are commonly used in baking and beer-brewing. With sufficient food, these yeast cells will divide after approximately 100 minutes [132]. In the absence of food cells begin to starve, which induces substantial cell changes; for instance, yeast cells grow spores to spread their progeny to new regions [132]. The level of nutrients present therefore influences the cellular behavior, and is an important parameter in biophysical studies. Furthermore, cellular activity varies wildly in time with respiration occurring in periodic bursts [133]. The period of cyclic processes varies substantially; *Saccharomyces cerevisiae* yeast exhibits both 40 minute and daily cycles in activity [133]. Consequently, the results of a wide range of cellular experiments can be expected to fluctuate with similar period. As such, analysis of a measurement conducted over a short time does not necessarily allow determination of the average cellular properties. Furthermore, substantial cell-to-cell variations must be accounted for if attempting to estimate average cellular parameters. Cell-to-cell variations can be severe for a wide range of measurements; for instance, measurements of cell adhesion to a substrate find the variance between cells to be comparable to the mean adhesion force [134].

Quantum metrology experiments are also typically performed in environments which are optimized for the optical apparatus. The fields usually propagate through free-space or optical fiber, with optical losses and spatial distortion minimized throughout. However, any truly practical application of quantum metrology to biology will need to operate in biologically relevant conditions. In many instances, cellular or sub-cellular samples cannot survive being dried out in air, and should be studied while in an aqueous environment. Most focusing optics suffer aberrations when focusing into water, as they are not designed to operate with an elevated refractive index. This
Figure 10: Layout of quantum OCT. The nonlinear crystal (NLC) generates entangled photon pairs, with one photon passing through a reference arm while the other illuminates the scattering sample. When the photons are recombined, two-photon interference only occurs for photons which follow a similar optical path length. Measurement of this interference thus allows an image to be constructed only using photons which have scattered from a specific depth in the sample. Conventional OCT applies short coherence length light to achieve a similar depth resolution. Reproduced from Ref. [138] with kind permission from Springer Science and Business Media.

degraded precision and resolution, and is an important limitation in many classical studies [112]. Furthermore, cells have a highly inhomogeneous refractive index [135, 136], which leads to both substantial distortion of transmitted fields [16] and relatively large scattering loss [137]. This loss degrades non-classical states, and limits the achievable enhancement in precision (see Section 4.5). Furthermore, it is important to ensure that the measurement efficiently samples the spatial mode of the probe field [35] (see Section 5.1). The presence of a large unknown distortion can lead to non-optimal sampling of the field, with a consequent reduction in the measurement efficiency. This is equivalent to the addition of loss, which further degrades the achievable quantum enhancement.

7. Progress in biological quantum metrology

7.1. Quantum optical coherence tomography

The first application of engineered quantum correlations in biology was in a demonstration of optical coherence tomography (OCT) with entangled
photons [14]. Classical OCT is a technique that is widely used for medical diagnosis [30, 139], where it is employed to generate high-resolution 3D images of such structures as the eye and the retina [140], and for dermatology [141] and cardiology [142]. OCT is based on a Michelson interferometer, with interference measured between a reference arm and backscattered light from a specimen. Axial resolution is typically provided by using white light with a short coherence length, such that interference only occurs for light which has backscattered at a specific depth in the sample. Since this relies on broadband white light to provide ultrashort coherence lengths, dispersion within the sample can substantially broaden the axial sectioning resolution.

In quantum OCT entangled photon pairs produced in parametric down-conversion are used instead [138, 143, 144]. Axial resolution is provided by HOM two-photon interference [44], which occurs when the back-scattered and reference arms are of equal length (as described in Fig. 2). Scanning of the reference arm therefore scans the depth of the measured image (see Fig. 10). When compared to the use of low coherence light, this can provide both superior axial resolution and immunity to dispersion [143, 144]. This quantum approach to OCT was applied to imaging of onion skin cells in Ref. [14]. However, shortly afterwards Ref. [145] demonstrated that the improved resolution and immunity to dispersion demonstrated in quantum OCT could also be achieved with uncorrelated light. The use of classical illumination could also allow a much higher photon flux and corresponding improvement in sensitivity. On a per photon basis, however, the classical technique falls far short of quantum OCT. As such, quantum OCT may see revived interest once the technologies required to produce and measure a high flux of entangled photons are developed. In its current form, it has primarily been useful for the innovations it brought to both quantum measurements and OCT [138].

7.2. Sensing the refractive index of protein solutions with NOON states

Following this application in OCT, entangled photons were applied to measurements of protein concentration in a microfluidic device [15]. A 2-photon NOON state was passed through a Mach-Zehnder interferometer with a microfluidic channel passing through one arm. A standard interferometric phase measurement was then used to infer the refractive index of the fluid within the channel (see Section 4.4). Proteins within solution were measured via the increase in the fluid refractive index.
In this case, the use of entangled photons increases the phase sensitivity, in principle allowing measurement precision which would classically require increased photon flux. Biological samples are generally photosensitive, and in some cases increasing the photon flux could damage the specimen (see Section 6.4). While entanglement was shown to improve the interferometer visibility beyond the threshold for supersensitivity, the experiment suffered from low detection efficiency and was unable to overcome the standard quantum limit. More importantly, the flux of measured photon pairs (0.1 s$^{-1}$) was far below any known damage threshold in biology. Consequently, even with improved technology, similar experiments are not likely to out-compete classical sensors which use high flux coherent light. This demonstration helped to show that quantum correlated light can benefit biological sensing, though it does not establish a clear route toward practical applications of quantum measurement in biology.

7.3. Squeezed light enhanced particle tracking

Quantum metrology has also been applied to enhance precision in optical tweezers based biophysics experiments in Refs. [16] [17]. Particle tracking in optical tweezers has revolutionized the field of biophysics by allowing characterization of single-molecule dynamics. This has enabled a vast array of discoveries, including both the dynamics and magnitude of the forces ap-
plied by biological motors [146, 147], the stretching and folding properties of DNA and RNA [111, 148], the dynamics of virus-host coupling [149], and the mechanical properties of cellular cytoplasm [150, 151, 152].

The particle position in optical tweezers is estimated from a laser beam deflection measurement. Such deflection measurements can be enhanced via the use of squeezed light [35, 39] (see Section 4.3), and Ref. [153] proposed use of a similar technique to enhance the precision of optical particle tracking. However, the relevant frequency range of optical tweezers based biophysics experiments is typically in the Hz–kHz range (see Section 6.3), while most squeezed light sources provide an enhancement in the MHz frequency regime (see Section 4.3). To address this, an optical lock-in detection scheme was developed to shift the low frequency particle tracking information into the MHz squeezing band without loss of precision [154].

Following these developments, Ref. [16] integrated squeezed light into optical tweezers to track microscopic particles below the quantum shot noise limit, using the apparatus shown in Fig. 1[11]. This experiment relied on an interferometric measurement of a weak scattered field [137], and can thus be considered with a similar framework to interferometric phase measurement (see Section 4). Quantum enhanced precision was demonstrated by producing the local oscillator in a bright squeezed state, which allowed a fixed 2.7 dB enhancement over the quantum noise limit (see Section 4.3).

Since this approach enhances the precision of optical tweezers based particle tracking, it could in principle be applied in any of the applications of optical tweezers. It is important to note, however, that thermal noise in the motion of the trapped particle limits the sensitivity of many optical tweezers applications, including biomolecular force sensing. For such applications, quantum enhanced precision does not typically provide a practical benefit. As such, this technology is primarily useful for shot-noise limited measurements such as studies of high-frequency processes, or in such experiments as microrheology where the thermal motion itself provides the signal [56].

7.3.1. Quantum enhanced microrheology

This quantum optical tweezers apparatus was used to track the thermal motion of naturally occurring lipid granules within *Saccharomyces cerevisiae* yeast cells, with amplitude squeezed light yielding a 2.4 dB enhancement in displacement sensitivity [16]. The cellular cytoplasm is crowded with large molecules, polymer networks, and various other organelles which confine the particle and influence the thermal motion [155]. The mechanical properties
of the cellular cytoplasm could be determined by characterizing this thermal motion, with quantum enhanced sensitivity allowing a 22\% improvement in precision over that achievable with coherent light (Fig. 12). This level of enhancement allows dynamic changes in the intracellular mechanical properties to be measured with 64\% improved temporal resolution. Alternatively, it allows the optical power to be reduced by 42\% without compromising sensitivity. Importantly, since this apparatus used a bright squeezed state, it could achieve absolute precision which was comparable to many similar classical microrheology experiments [152, 156], though state-of-the-art microrheology experiments achieve over an order of magnitude greater displacement sensitivity [157].

7.3.2. Quantum enhanced scanning probe microscope

The quantum optical tweezers apparatus was then applied to spatially resolve cytoplasmic structure in Ref. [17]. Spatial imaging was achieved using a technique called photonic force microscopy [158, 159], in which spatial variations in the local environment are sampled by a small particle as it slowly moves through the cell. A profile of the structure is then constructed from the influence of the structure on the thermal motion. This approach to imaging is closely analogous to that taken in atomic force microscopy, though here
a trapped bead acts as the probe tip. In both cases, the use of a scanning probe means that spatial resolution is limited by the signal-to-noise ratio rather than the diffraction limit \cite{159,160} (see Section 5). Thus, the use of squeezed light to improve sensitivity can also enhance resolution.

This approach was used in Ref. \cite{17} to construct profiles of spatial structures within a living yeast cell (Fig. 13). In this experiment, particles were only tracked along the \( x \) axis, while the particles diffuse along all three. As such, the constructed profiles follow the projection of an unknown trajectory onto the \( x \) axis. For any practical application of this technique, 3D imaging is required. However, this experiment demonstrated both sub-diffraction-limited quantum metrology and quantum enhanced spatial resolution for the first time in a biological context. Spatial structure within a living yeast cell was observed at length scales down to 10 nm, far below the diffraction limit and comparable to that achieved in similar classical photonic force mi-
croscopy experiments \cite{161, 162}. Squeezed light was found to enhance the spatial resolution by 14% over that achievable with coherent light. This was the first demonstration that squeezed light could be used to improve resolution, though such a resolution enhancement has been proposed for far-field optical imaging \cite{163, 164}. The absolute enhancement in resolution was relatively small, due to the relatively modest degree of available squeezing. If combined with state-of-the-art squeezed light with over 10 dB of measured squeezing \cite{59, 36, 64}, this technique is predicted to allow up to an order of magnitude improvement in resolution over similar classical imaging techniques \cite{17}.

These were the first experiments to apply squeezed light in biological applications. They demonstrated an enhancement in particle tracking precision over that possible with coherent light using a device which was comparable to those used in biophysics experiments, though constrained by the use of low numerical aperture objectives \cite{165}. With some improvements to the design, it is feasible that a quantum optical tweezers apparatus based on this approach could outperform classical technology. This could benefit a range of important biophysical applications of optical tweezers.

### 7.4. Optical stimulation with number states of light

Each of the experiments described above relied on non-classically correlated light to very gently probe a biological system, with the aim of observing it while introducing minimal disruption. In Ref. \cite{7}, Teich and Saleh discussed a completely different approach to quantum metrology in which non-classical light could be used to stimulate retinal rod cells. Rod cells are biological detectors which produce electrical signals in response to optical stimulation, and are sensitive at the single-photon level \cite{166, 167}.

Previously, the electrical response of rod cells to illumination has been characterized using classical light sources. The photon statistics of such light sources inevitably introduces uncertainty to the illuminating photon number. When studying single-photon responses, the variance is comparable to the mean photon number. Consequently, a single-photon response can only be unambiguously observed if it can be resolved from the zero-photon response and two-photon response. In some species, the electric response of rod cells to optical stimulation allows discrimination of the single-photon response \cite{166, 167}. In other species, however, the electric signal from the rod cells does not allow the single-photon response to be separated reliably, and the single-photon response can only be inferred statistically. As discussed in
Ref. [7], non-classical states of light could be used to suppress the statistical uncertainty in the optical stimulation, thus improving characterization of the retinal response.

Such a scheme was demonstrated very recently, with single photons used to stimulate retinal rod cells from *Xenopus laevis* toads [18]. In this work, parametric down-conversion was used to generate entangled photon pairs at the visible wavelength of 532 nm. One of these photons was collected and directed onto the rod cell. This photon was heralded with detection of the second photon, such that apart from detector dark counts all uncertainty in the photon arrival statistics is eliminated. This allowed the single-photon sensitivity of the cells to be directly confirmed in a species for which the electrical response itself does not allow photon resolution, and enabled a precise determination of its quantum efficiency. It further allowed the transient response of the cell to a single photon to be characterized without relying on statistical inference to estimate which detection events correspond to single photons.

This preliminary work established the possibility of non-classical optical stimulation for biological experiments. Such a technique could potentially allow important advances in the study of eyes, particularly when performed with a more intricate neural network. The uncertainty intrinsic to classical stimulation is compounded as the electrical response from multiple rod cells are combined and processed at the ganglion nerve cells [168], with photon statistics contributing significant variations to the resulting neural signal transmitted to the brain [169, 170]. Consequently, Ref. [7] proposed the use of non-classical stimulation of rod cells to study the responsive properties of ganglion nerve cells.

Furthermore, this utilizes a biological sample as a photodetector, which maps the photonic state to an electrical state in the detector (see the discussion of photodetection in Section 3). This provides a method to map non-classical correlations into a biological system. If these correlations could be observed after introduction to the cells, the decoherence of the quantum state could be quantified. This would open new possibilities for biological studies; in particular, it could be relevant to studies of photosynthesis where experimental evidence suggests that quantum coherence is present in the light harvesting process [171, 172]. Although these experiments have presented evidence for coherence, so far there has been no test which could provide an unambiguous witness of this quantum coherence. Additionally, there have been further suggestions that entanglement may also be present.
and provide enhanced collection efficiency \[173\], which has inspired lively debate \[174\]. Observation of the evolution of a quantum state could provide a witness to the coherence properties of photosynthesis, and might therefore provide important new insights into such systems \[175\].

8. Promising technologies for future biological applications

With these demonstrations, quantum measurements of biology are no longer a future perspective but are a current reality. In addition to the applications already demonstrated, there are also a wide range of other quantum measurements which may very soon hold important applications in biology. This review now turns to these future applications.

8.1. Entangled two-photon microscopy

Two-photon microscopy is an area in which entangled photons could provide a substantial practical advantage \[22, 176\]. In two-photon microscopy, two-photon absorption within a sample is studied via its specific fluorescent signature. Since this is a third-order nonlinear optical process, two-photon absorption will typically occur only near the central focus of the illumination. When compared to one-photon absorption, this both sharpens the spatial resolution and suppresses fluorescence away from the focal plane. However, classical two-photon absorption is an extremely inefficient process requiring a very high input flux of photons. The peak power is typically maximized by use of high-peak-intensity pulsed lasers, which can damage the specimen \[91\].

If highly correlated photon pairs are used instead of classical light, the two-photon absorption rate can be vastly enhanced, with the absorption process depending linearly rather than quadratically on the photon-flux density \[177\]. Qualitatively, this enhancement occurs because the rate of two-photon absorption is proportional to the flux of coincident photon pairs; for uncorrelated light, this flux scales as the square of the power, while entangled photons can always arrive in coincident pairs, such that the flux scales linearly with the power. This can also be expressed with the photodetection framework introduced in Section 3. In this case, the entangled photons are produced in two separate spatial modes by parametric downconversion, with the overall state

\[
|\Psi\rangle = \sqrt{1-\epsilon} |0\rangle_1 |0\rangle_2 + \sqrt{\epsilon} |1\rangle_1 |1\rangle_2, \tag{72}
\]
where higher photon number terms have been neglected. For this state, two-photon absorption from the two modes occurs with a rate of

$$R_{12}^{(2)} \propto \langle \hat{a}_1^{\dagger} \hat{a}_2^{\dagger} \hat{a}_2 \hat{a}_1 \rangle = \epsilon.$$  (73)

This scales linearly with the incident power, since $$\langle \hat{n}_1 \rangle = \langle \hat{n}_2 \rangle = \epsilon$$. Using this in Eq. (21), one can see that the second order coherence function is given by

$$g_{12}^{(2)} = 1/\epsilon.$$  In the limit that $$\epsilon$$ is small, $$g_{12}^{(2)}$$ can be very large, which indicates a large enhancement in two-photon absorption over the use of coherent light. At high flux, however, the two-photon absorption rate can be comparable for coherent and entangled illumination. This enhancement requires the flux to be low relative to the saturation of the two-photon transition; a condition which is almost always met.

The enhanced absorption of entangled photon pairs allows multi-photon fluorescence microscopy to proceed with intensities more suited to biological samples. For instance, recent demonstrations in non-biological organic chemistry have found that the two-photon absorption and two-photon fluorescence measured with an entangled photon flux of $$10^7 \text{ s}^{-1}$$ is comparable to similar measurements with $$10^{17} \text{ s}^{-1}$$ coherent photons, allowing a 10 order of magnitude reduction in power from tens of mW to a few pW [178, 179]. In principle, an entangled light microscope could also allow superior resolution to that achievable classically [101], though this has not yet been demonstrated (see Section 5).
Furthermore, entangled photons reveal information about the nonlinear absorption mechanism which is inaccessible to classical light sources. Two-photon absorption can occur either via a permanent dipole transition or via a virtual state transition \([180]\). While these transitions are classically indistinguishable, the different mechanisms have a markedly different response to entangled photons; dipole transitions are not enhanced by the entanglement \([23]\), while entangled photons that are phase-matched to virtual states are absorbed at a vastly enhanced rate \([177, 181]\). Even among transitions mediated by virtual states, the entangled photon absorption cross section is not proportional to the classical absorption cross section, as the enhancement depends on the detuning and linewidth of the virtual state \([182]\). The two-photon transition amplitudes contributed by the entangled photons can also interfere, producing “entanglement-induced transparency”, analogous to electromagnetically induced transparency \([176]\). An entangled two-photon microscope may prove the only tool capable of probing the properties of virtual states.

Although this has not yet been applied in biological measurements, these preliminary results suggest that entanglement could be extremely promising in future two-photon microscopy applications. It could both enhance the visibility in two-photon fluorescent microscopy, and reveal classically inaccessible information.

### 8.2. Quantum super-resolution in fluorescence microscopy

While the non-classical states used in most quantum metrology experiments require sophisticated state preparation, systems such as fluorescent particles naturally emit non-classically correlated light. These quantum correlations are ignored in classical experiments, though recent results have shown that measurement of the correlations provides additional information that can be used to enhance spatial resolution \([183]\). In classical fluorescent microscopy, the optical diffraction limit restricts the resolution with which fluorescent particles can be distinguished to approximately half the wavelength of light (see Section \(5.2\)). While a number of techniques have been developed to overcome this limit, almost all rely on optical nonlinearities in the fluorescent particle, and therefore require relatively high illuminating power (see Section \(5\)). Furthermore, these approaches are based on a scanning point focus, and therefore lack the speed of parallel imaging \([184]\). The only exception is structured illumination, which only requires the illuminating field to be controllably modulated to shift high spatial frequency
patterns into the measurable range. This approach allows the resolution to be halved, and has become an important tool in biological microscopy [98], enabling for instance direct imaging of molecular motor dynamics in living cells [184]. Broadly speaking, while other techniques use nonlinearities to provide more resolution information, structured illumination can be thought of as a technique to capture information which is always present and usually neglected.

In a similar manner, photon statistics can also be measured to capture more of the information from the fluorescent emission. In fluorescence microscopy, a fluorescent particle absorbs energy as it is excited to a higher state, and is then imaged as it decays back to the ground state by re-radiating at another wavelength. This mechanism generally only allows emission of one photon at a time, which results in photon anti-bunching and associated non-classical photon correlations (see Section 3). When multiple photons are simultaneously measured, they must have originated from separate fluorescent centers. This provides an additional method to discriminate the emitted fields of closely spaced emitters which can be used to enhance resolution.

This concept has been applied in two separate approaches to resolve fluorescent particles below the diffraction limit. In Ref. [24] the positions of fluorescent particles was estimated from both the intensity profile and the coincident detection events. The intensity profile and the coincident detection events both contributed information which could be used to statistically estimate the fluorescent center locations. Such an estimation procedure is a class of image deconvolution [88] (see Section 5.2), with the measurement of photon coincidences providing information that is not available in classical deconvolution methods. In principle this allows improved resolution, though to date the achievable improvement in the statistical estimation has not been quantified.

A related approach was also demonstrated in Ref. [25]. In that work a large collection of fluorescent particles were excited with pulsed light and simultaneously measured in wide-field imaging. With this configuration, the fluorescent particles could only emit one photon each per excitation pulse. Consequently, multi-photon detection events could occur only when multiple emitters were separated by less than the diffraction limit of the microscope. For locations with only a single emitter, the measured light is highly anti-bunched, with a second order coherence function which ideally reaches \( g^{(2)}(0) = 0 \) (see Section 3). By contrast, the light from multiple co-located emitters is only weakly anti-bunched. The anti-bunching can be quantified
Figure 15: Super-resolution via measurement of photon coincidence statistics. Fluorescent particles are illuminated with short pulses of laser light, and the resulting fluorescence is measured on a high efficiency camera. Each pulse is sufficiently fast that a particle can only be excited once per pulse, and each coincident photon must originate from a different fluorescent particle. An analysis of the $N$ photon coincidences then allows a $N^{1/2}$ enhancement in resolution, with example data shown at the right. This shows the $N = 1$, which is simply the intensity profile, the $N = 2$ and the $N = 3$ data. As $N$ increases the resolution is visibly improved, though the contrast is degraded. Reprinted with permission from Ref. [25]. Copyright (2013) American Chemical Society.
by the parameter \(1 - g^{(2)}(0)\), which drops to zero for uncorrelated light. By measuring both the 1 and 2 photon coincidences at each pixel, the spatial profile of both anti-bunching and intensity can be determined. Together, these allow the square of the single-photon emission probabilities to be mapped out. When compared to the intensity image, which represents the profile of single-photon emission probabilities, this allows a resolution enhancement of \(2^{1/2}\). 

This can also be extended to higher order correlations, with measurements of 1 to \(N\) coincident detection events at each pixel allowing the \(N\)th power of the single-photon emission probabilities to be mapped, with a resulting \(N^{1/2}\) enhancement in resolution [183]. This was demonstrated experimentally with photon coincidences measured up to \(N = 3\), which allowed the spatial resolution to be enhanced from 272 nm to 181 nm [25]. A very recent extension of this technique has shown that theoretically unlimited resolution is achievable with improved analysis [185]. This is because each fluorescent center can only emit a single photon, so provided one can estimate the number of fluorescent centers within a region of the image, one can reasonably assume that there are no higher number photon coincidences. Under this assumption, measurement of the 1 to \(N\) photon coincidences is sufficient to reconstruct the photon emission probabilities to arbitrarily high order. In this scenario, the resolution becomes limited only by the statistical uncertainty in the determination of the 1 to \(N\) photon coincidences [185].

Since this approach involves parallel imaging, it can in principle proceed at high speed and with extremely narrow resolution. This enhancement could hold practical significance, just as structured illumination is already used in important biological applications. Furthermore, applying this method in conjunction with nonlinearities or structured illumination could potentially combine the resolution enhancements, which would allow this technique to resolve smaller features than any directly comparable classical technique.

8.3. Differential interference microscopy

Quantum metrology can also provide enhanced sensitivity in differential interference microscopy, which is another technique that is widely used for biological imaging. In such measurements, a light beam is split and focused through two slightly different sections of a sample. The phase difference between the paths is then measured to determine differences in the refractive index along differing paths. This can then be used to reconstruct the spatial profile of the refractive index within the sample [186].
Phase measurements have been enhanced with quantum correlated light for some time, which suggests that phase contrast microscopy can also be enhanced with quantum correlated light. The feasibility of this was demonstrated in Ref. [27], where two photon NOON states were used to allow sub-shot noise imaging. In this case, the two photons occupied one of the two linear polarizations, and were separated with polarizing optics. Both polarization modes were then focused through a sample, and slight differences in the two paths measured via its effect on the relative phase. A full image could then be reconstructed by raster scanning over the sample.

A closely related approach was later taken in Ref. [28]. In this case, the relative phase between two orthogonal polarization states was measured to image sample birefringence. In both of these experiments, high losses degraded the entanglement to the point that post-selection was required to observe any quantum enhancement. Additionally, both the sensitivity and spatial resolution were far inferior to comparable classical techniques. However, an extension of this technique which applies high flux quantum correlated light with classically optimized spatial resolution would provide an extremely useful tool for biological research.

8.4. Absorption imaging

Absorption imaging constitutes the staple application of optical microscopy, and is routinely used in a vast array of biological applications. Recently, absorption imaging with quantum enhanced precision has been demonstrated in two separate configurations [26, 187, 86]. The first approach used heralded single photons to estimate the profile of a weakly absorbing object. Absorption measurements are distinct from phase or amplitude measurements, since the presence of absorption necessarily couples in vacuum fluctuations to the detected optical field (see Section 4.5). However, the detection statistics of this experiment can be understood with the simple semiclassical framework of Section 2. When light is incident on an absorbing sample, the loss can be estimated from the resulting reduction in photon flux. Any classical light source is subject to statistical fluctuations which enforce a minimum uncertainty in the incident photon number of \( \langle n_{\text{sig}} \rangle^{1/2} \), given the average flux \( \langle n_{\text{sig}} \rangle \). Consequently, the sample must absorb at least \( \langle n_{\text{sig}} \rangle^{1/2} \) photons to be statistically observable. This limit was overcome in Refs. [26, 187] by using parametric down-conversion to produce entangled photon pairs. The photons impinging on the sample were then heralded with measurement of the twin photon, thereby eliminating the statistical uncertainty in the incident
photon number. This allowed the signal-to-noise ratio to be improved by 30% within a multi-mode parallel optical imaging experiment.

In the second approach, the shape of a completely absorbing mask was estimated using the noise properties of multimode squeezed vacuum. Twin multimode squeezed states were generated via 4-wave mixing in an atomic vapour, with one beam providing a reference while the other propagated through an absorbing mask. The noise variance of the vacuum fields were then measured using homodyne measurements, and the loss in the signal field estimated via the degradation of the squeezed state (see Section 4.5). Homodyne measurement only samples a single mode of the field, and the shape of this mode can be set arbitrarily by reshaping the reference field. The loss in a range of spatial modes could therefore be estimated by adjusting the reference field, which eventually allows reconstruction of the profile of the absorbing mask. To provide a classical benchmark, this strategy was compared to a similar procedure using thermal light with excess classical noise; as the loss in the mode increases, the classical noise is reduced. This comparison showed that squeezed vacuum provided far improved accuracy in the reconstructed images.

While most measurements rely on first order statistics (i.e. the mean signal), this strategy is based on second-order measurement statistics (the variance of the measured amplitude). This experiment demonstrated that entanglement could enhance the estimation precision of such a second-order estimation. However, it remains to be shown whether these results surpass a simple first-order measurement, such as direct imaging of the transmitted intensity. Quantum imaging with squeezed vacuum will only see practical applications if it can surpass direct imaging, which is the standard method for absorption imaging.

While neither of these experiments achieved absorption imaging with microscopic resolution, they established two distinct technologies which could each be extended to perform biological absorption microscopy.

9. Spin based probes of relevance to biology

While the discussion so far has focused entirely on optical measurements, quantum metrology is also performed with non-optical systems. In particular, non-classical spin states are a promising technology for future applications. Although such states have not been discussed in this review, a quantum treatment of spin-based measurements follows a similar treatment to that
in Section 4, with precision limits given by the quantum Fisher information (Section 4.1). A comprehensive review of spin based quantum metrology is beyond the scope of this work, and would warrant an entire review in its own right. Here we briefly overview some technologies which are likely to hold future applications of biological quantum metrology.

9.1. Atomic magnetometers

The development of high sensitivity magnetometers capable of measuring biomagnetic fields has both advanced biological research and enabled new methods in medical diagnosis. In particular, such studies have provided rich information about the function of the heart [188] and brain [189], which both produce a relatively large biomagnetic field. These measurements have typically been carried out with a superconducting quantum interferometric device (SQUID), which uses interference in a superconducting circuit to sense magnetic fields with extreme precision [190]; mostly because for a long time the SQUID was the only magnetometer sensitive enough for useful biomedical applications. To maintain its superconducting circuit a SQUID requires cryogenic cooling, making it bulky and expensive. This limits the clinical applications described above to large and well-funded institutions [191].

With recent advances, atom based magnetometers can now provide the sensitivity of a SQUID while operating at room temperature [192, 193, 32]. As such, atomic magnetometers are used in the above mentioned biological applications, measuring both the dynamics and spatial profile of the biomagnetic field generated by a beating heart [194, 195, 196] and neural activity in the brain in response to stimuli [197, 191]. Magnetic resonance imaging (MRI) is another important application which has previously required cryogenic cooling of superconductors [198]; either in the form of superconducting magnets to produce the fields, or a SQUID to measure the low-field MRI signal. Now, atomic magnetometers have been applied to allow cryogen-free low-field MRI [199].

9.1.1. Quantum limits to sensitivity

Atomic magnetometers are based on optical manipulation and readout of the spin state of an atomic ensemble in the presence of a magnetic field. Light that is near-resonant with an optical transition spin polarizes the hyperfine levels of the ground state, which subsequently undergo Larmor spin precession in the magnetic field. The phase and amplitude of the transmit-
Figure 16: Layout for QND atomic magnetometry. A pump field is used to spin polarize an atomic vapor. After this a probe field is passed through the cell, and the magnetic field estimated from the Faraday polarization rotation. Reproduced with permission from Ref. [200], Copyright (2010) by The American Physical Society.

ted light then encodes information about the spin precession, from which the magnetic field can be estimated.

The sensitivity of this measurement is fundamentally limited by quantum noise in both the optical readout and the spin of the atomic ensemble. Quantum noise in the spin states, referred to as projection noise, results from the projection of the atomic spin onto the measurement axis. The mean spin is oriented orthogonal to the measurement axis to provide optimal estimation of the spin precession. Projection noise then follows from the statistical fluctuations in the measurement. The optical readout can also be limited by quantum shot noise. While the dominant source of quantum noise depends on the details of the measurement, the contributions of projection noise and optical shot noise are comparable when the measurement is optimized [201].

9.1.2. Enhancement with entangled atoms

There has been much interest in the possibility to improve sensitivity beyond the projection noise and shot noise limits. Optical readout of the Faraday polarization rotation is a quantum non-demolition (QND) measurement of the spin polarization state along one axis [200]. In a QND based magnetometer, each measurement both provides information about the magnetic field and projects the system onto a spin-squeezed state, increasing the sensitivity of subsequent measurements.

An early theoretical analysis suggested that quantum correlations within the spin ensemble would be destroyed by spin relaxation, rendering spin squeezing effective only for measurements much shorter than the spin-relaxation
Figure 17: Measurements with spin squeezing. The measurement statistics of QND measurements were studied, first with no atoms in the trap to characterize the readout noise (a) and then independently prepared coherent spin states (b), with the measured distribution corresponding to the projection noise. The solid curves indicate $2\sigma$ radii for Gaussian fits. (c) When a single coherent spin state is prepared and sampled sequentially, the successive measurements squeeze the spin variance below the projection noise limit (dashed circle) along one axis. Reproduced with permission from Ref. [202], Copyright (2012) by The American Physical Society.

9.1.3. Use of quantum correlated light

In addition to the enhancement by spin squeezing, non-classical states of light have also been used to overcome the quantum noise on the optical readout [29, 40, 207]. The optical magnetometer in Ref. [29] achieved sensitivity better than the shot-noise limit using a polarization-squeezed probe tuned near the atomic resonance. In that work, however, the atomic vapor was not spin polarized, but instead kept in a thermal state, which resulted in poor absolute sensitivity. A similar experiment was reported later in Ref. [40], with
the absolute sensitivity vastly improved and the frequency range of squeezing extended into the biologically relevant sub-kHz regime. Such an enhancement could be particularly important once it is applied in a QND based magnetometer, because it acts both to improve the measurement sensitivity and also to improve the spin squeezing. Overall, this improves the fundamental limit on sensitivity for a QND based magnetometer \[201, 29\]. To achieve this, it is important that there is no increase in spin decoherence induced by the probe when using quantum correlated light. To test for additional decoherence, Ref. \[207\] applied two-photon NOON states to perform optical readout in atomic magnetometry. By characterizing the photon scattering and atomic excitations, they could verify that entangled light induced less decoherence in the spin state than coherent light which achieved the same sensitivity.

By using squeezed light in a QND measurement to condition the spin-states of the atomic ensemble, it should be possible to achieve extremely high sensitivity. Once this is achieved in state-of-the-art magnetometers, the magnetic field sensitivity can be expected to outcompete SQUIDs, and have important biological and clinical applications.

9.2. Nitrogen vacancy centres in diamond

One of the key factors that enables spin polarisation, spin coherence, and quantum correlations to be established in the atomic magnetometers dis-
cussed in the previous Sub-Section is that dilute gases of atoms are naturally well isolated from their environments and therefore from possible quantum decoherence channels. However, this limits applications in biology to scenarios where the atomic ensemble is also well isolated from the biological specimen, typically confined within a millimetre to centimetre sized gas cell [208]. This prohibits the nano- or micro-scale resolution crucial for a great many biological applications (see Section 6.1). An alternative approach is to use solid-state artificial atoms such as quantum dots or fluorophores as quantum probes, which are typically embedded within a crystalline host material. These can allow the close proximity required for nanoscale resolution, either by placing the biological specimen in direct contact with the substrate [209], or embedding a probe nanocrystal within the specimen [210, 211].

While this close proximity allows nanoscale resolution, it also introduces significant environmental coupling to the state which results in strong quantum decoherence. Substantial advances have been made in reducing this decoherence by controlling the material properties of the host, most particularly its structural and chemical purity and surface quality; by employing control techniques such as dynamical decoupling to suppress the effect of environmental spin noise [212]; and by identifying artificial atoms that display intrinsic shielding from their environments. Even so, cryogenic conditions are still required to achieve appreciable spin coherence with the majority of solid-state quantum probes [213, 214]. Nitrogen vacancy centres in diamond are a notable exception, exhibiting long spin coherence times even at room temperature [212]. Combined with optical addressability, biocompatibility [215], and photostability [216], this presents unique opportunities for biological applications in quantum metrology which we briefly introduce in this Section.

9.2.1. Basic properties of nitrogen vacancy centres

The nitrogen vacancy (NV) centre naturally forms as a defect in diamond when two nearest-neighbour carbon atoms are displaced, with one site filled with a nitrogen atom and the other left vacant (see Fig. 19). The defect has two charge states, a neutral NV\(^0\) state and a negative NV\(^-\) state. The NV\(^-\) state is particularly favourable for quantum metrological applications, featuring spin-triplet ground and excited states that can be conveniently accessed via optical transitions at wavelengths near 637 nm as shown in Fig. 19(b). Very long spin coherence times of 0.6 s and 1.8 ms have been achieved at 77 K [212] and room temperature [217], respectively. The optical
transitions allow both control and read-out of the spin state of the NV. Perhaps most significantly, due to non-radiative transitions that connect the \( m_s = \pm 1 \) excited states to the \( m_s = 0 \) ground state, broadband optical illumination is sufficient to spin polarise the NV into its \( m_s = 0 \) ground state. Microwave fields can then be used to coherently drive transitions between the \( m_s = 0 \) and \( m_s = \pm 1 \) ground states; while significant differences between the fluorescence from the \( m_s = 0 \) and \( m_s = \pm 1 \) levels allows accurate read-out of the NV spin state \[218\].

9.2.2. In vivo thermometry and field sensing

The ability to initialise, control, and readout spin states, are the key requirements to realise both magnetometry and electrometry with nitrogen vacancy centres \[219\]. The exquisite sensitivity possible is clearly illustrated by the demonstration of nanoscale magnetic imaging of a single electron spin at room temperature \[220\]. In that experiment, Zeeman-shifts in the NV electronic spin resonance frequencies due to the electron spin were read-out using optically-detected magnetic resonance (ODMR). Similar approaches have recently been applied in two experiments to perform NV-based magnetometry of biological systems. In the first, individual fluorescent nanodiamonds were introduced within living human HeLa cells and their orientation was tracked.
via continuous ODMR [210]. In the second, ODMR was used to characterise the magnetic field of living magnetotactic bacteria [209]. The bacteria was placed upon a diamond chip in close proximity to a thin NV layer, allowing the magnetic field of the bacteria to be characterised with 400 nm resolution (see Fig. 20).

While the ODMR measurements in Ref. [210] were used to track the nanodiamond rather than extract meaningful information about the magnetic properties of the cell, the same reference experimentally demonstrated the technique of quantum decoherence sensing [221, 222]. Such sensing seeks to take advantage of the extreme sensitivity of the coherence time of qubits to learn something of the nature of their environment. Ref. [210] probed the coherence time of the spin of an NV-nanodiamond within an HeLa cell using Rabi and spin-echo sequences. Subsequent work has used this approach to image microbiological structures within a diamond microfluidic channel [223]. Here, the approach is to introduce labels with large magnetic moments within the channel. In the absence of an external magnetic field, these labels freely diffuse. When in close proximity to an NV-spin, the stochastic magnetic field fluctuations they introduce act to decrease the NV coherence time. In Ref. [223] Gadolinium ions (Gd$^{3+}$) were chosen as the label due to their very large magnetic moment. This allowed microfluidic detection of as few as 1000 statistically polarised spins; as well as imaging of 150 nm thick microtomed sections of HeLa cells with 472 nm resolution, though this latter demon-
Nitrogen vacancy centres have also been utilised for nanoscale thermometry within living cells with a sensitivity of 9 mK Hz\(^{-1/2}\) [211]. In this experiment, the separation of the \(m_s = 0\) and \(m_s = \pm 1\) ground states of the NV-spin was accurately determined using a spin-echo sequence. This separation is linked to the temperature of the nanodiamond due to thermally induced lattice strain. The measurement used a nanodiamond containing an ensemble of approximately 500 uncorrelated NV spins, with the sensitivity correspondingly enhanced by a factor of \(\sqrt{500}\). This enabled superior sensitivity to all previous nanoscale thermometers, offering the prospect to study the nanoscale energetics of biophysical processes such as gene expression and tumour metabolism.

9.2.3. Quantum correlations

To date all biological experiments with NV centres have relied either on a single NV or an ensemble of uncorrelated NVs. As discussed in Section 4, in quantum metrology quantum correlations and entanglement can be used to suppress measurement noise, and ultimately improve how the measurement sensitivity scales with particle number. Such techniques could be particularly relevant to nanodiamond NV sensors, where the number of NV centres in the nanodiamond are constrained both by its physical dimensions and by NV-NV interactions that cause decoherence [224]. Quantum correlations between the 500 NV centres contained within the nanodiamond thermometer discussed above, for instance, could in principle yield over an order-of-magnitude improvement in sensitivity. Techniques capable of generating such correlations in an NV ensemble are currently under development [212]. For example, one method which is being considered is to use strain-induced resonance frequency shifts to couple multiple NV spins to the motion of a micromechanical oscillator [225]. This discussion is far from exhaustive; for a more detailed review see Ref. [219].

10. Conclusion

The field of quantum metrology broadly encompasses the use of quantum correlated states to enhance or enable measurements. This is motivated by two distinct goals. One aim is to establish the fundamental consequences of
quantum mechanics on measurements. Toward this end, the quantum limits on measurements and the strategies required to overcome them are both studied. The other aim of quantum metrology is to harness quantum effects to provide a practical benefit in measurement applications. The primary motivation for these experiments is to out-compete their classical counterparts in some manner. The best example of this is in gravitational wave observatories, where squeezed light is used to achieve sensitivity below the quantum noise limit \([11, 12]\). This is now routinely employed because it has proven to improve performance in absolute terms \([13]\).

This review has introduced quantum metrology from the context of biological measurements, with a specific focus on the practical advantages which can be gained, and it has provided an overview of both the advances already achieved and the future potential for biological quantum metrology. The technologies required for practical applications of quantum metrology have now been developed, as evidenced by its use in gravitational wave observatories. Although gravitational wave observation is an extremely important goal, it is also extremely specialized; only five observatories currently exist. Biological measurement has also been an important goal of the field since the 1980s, which encompasses an extremely wide range of potential applications. Recent advances in quantum technologies now allow applications in biological measurement, and proof-of-principle demonstrations have already used a wide variety of non-classical states within a range of biological experiments. Entangled photon pairs, photonic NOON states, bright squeezed states, and single photon states have enabled enhancements in tissue imaging, protein sensing, study of the mechanical properties of living cells, and study of the photodetection response of retinal rod cells (see Section \(7\)). Though these experiments have not yet outperformed state-of-the-art classical measurements, they have established the potential for quantum metrology to provide practical benefits to future experiments. Furthermore, they have demonstrated that quantum metrology is relevant to a wide variety of different measurement applications.

In addition to these demonstrations of biological quantum metrology, a range of other technologies have been developed recently which may soon be applied to biological measurements. These include microscopes which use entangled photons to probe two-photon transitions, super-resolution techniques which enhance resolution by studying the photon antibunching of fluorescent emission, both phase-contrast and absorption microscopy, magnetometry with quantum correlated atomic spins, and nanoscale field and
temperature imaging with NV centres (see Sections 8 and 9). This list is not exhaustive, and other quantum measurement technologies also hold future applications in biology. With further advances, biological quantum metrology has the potential to redefine the state-of-the-art, and is likely to have important applications for a wide range of measurements.

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