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Mini-Review

Open quantum systems theory of ultraweak ultraviolet photon emissions: Revisiting Gurwitsch's onion experiment as a prototype for quantum biology

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A B S T R A C T

A century ago it was discovered that metabolic processes in living cells emit a spectrum of very low intensity radiation. This was based on observations that radiant energy from proliferating cells can amplify the rate of cell division in other nearby cellular life. Although metabolic radiation is now thoroughly documented in research on ultraweak photon emissions (UPE), the original finding that UPE can enhance mitogenesis remains controversial. This controversy is addressed by establishing a physical basis for phenomenological observations that biological UPE can amplify mitogenesis in living cells. Enhanced mitosis is rationalized as a resonance effect based on open quantum systems theory using Fano and Feshbach's methods. This application of quantum theory to biology has important consequences for understanding health, medicine, and principles of living matter.

1. Introduction

Alexander Gurwitsch made fundamental contributions to physiology and medicine through his research on biophotons [1–4]. In his investigations of cellular replication, Gurwitsch observed that mitosis could be stimulated in living cells by non-chemical interactions with other cells in an effect which he attributed to "mitotic radiation" [5]. Known subsequently as mitogenetic radiation [1], these spontaneous ultraweak photon emissions (UPE) from living cells were not recognized scientifically until cellular radiation was systematically investigated with photomultiplier tubes (PMTs) in the following decades [3,6,7]. Numerous experiments have now confirmed the existence of UPE due to oxidative free radical processes [1,8]. Although mechanisms of cellular UPE generation remain unclear [9], it is now established that all living cells emit minuscule numbers of photons in the form of UPE as byproducts of biochemical reactions [3,10]. Nevertheless, the impact of such weak radiation on living cells remains a topic of intense scientific scrutiny and debate [1,11,12].

In his work, Gurwitsch theorized that mitogenesis—the initiation of cell mitosis—was controlled by two factors which coincide to initiate cell replication [1,13,14]:

1. The internal preparation of a cell in terms of its metabolic readiness for cell division.
2. The appearance of an external impulse or signal that prompts the cell to begin mitosis.

To test his hypothesis that the external signal which initiated cell replication was not chemical, but was rather a form of electromagnetic radiation [14], Gurwitsch carried out experiments on onion root cells by arranging two onions so that one root grew perpendicularly to the other, with the tip (apex) of the "emitter" root facing one side of the meristem of the "receiver" root (Fig. 1) [5]. Cells in the receiver root on the side of the emitter replicated significantly more than the cells on the opposite side (Figs. 2-3) [1].

Over the course of the next two decades (1923–1943), Gurwitsch and colleagues carried out a series of experiments on plants, animal tissues, yeasts, and bacterial cultures that culminated in the hypothesis that ultraviolet (UV) UPE could stimulate growth in living cells [14,15]. Gurwitsch and others found that cell replication could be induced by a weak 190–280 nm light source in receiver cells stored in darkness, or by UV light up to 326 nm in receiver cells co-illuminated by faint non-UV light [16]. Gurwitsch attributed induction of mitogenesis in cells that were co-illuminated by UV and visible light to the action of two-photon absorption effects [14,16].

Mitogenetic radiation from living cells (capable of inducing mitosis in other cells) was mainly found to be UV light in the 190–250 nm range based on observations performed using "biological detectors" [17,18]. Many other types of cells—besides onion root cells—were found capable of responding to mitogenetic radiation with enhanced cell replication [16]. Yeast cultures prepared in the lag phase of growth were especially convenient detector systems, whereas yeast cultures prepared in the exponential growth phase were found to be excellent sources [16]. It was concluded that mitogenetic radiation itself resulted from height-

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ened metabolic activity in dividing cells which could in turn stimulate metabolism in other cells [16].

The most well known spectrum of celluar UPE extends over 350–1300 nm to include UV, visible, and infrared (IR) regions of the electromagnetic spectrum [19]. These emissions result from excited electronic processes that occur during peroxidation reactions involving lipids, nucleic acids, and proteins [10,20]. Reports of UV UPE sources in the 210–390 nm spectrum are attributed to oxidative side-reactions that accompany protein synthesis [21,22] such as radical recombination reactions that occur during oxidative deamination [23,24]. Much like UPE in the 350–1300 nm range which are associated with oxidative stress [20], the 190–250 nm region of UPE from living cells has been linked to glycolysis, high-energy oxidation reactions, peptide-bond cleavages, and phosphatase-mediated reactions [17].

In addition to such known metabolic processes, Gurwitsch hypothesized a functional role for certain photochemical excited states that comprise common energy levels along which energy quanta might migrate or undergo "summation of quanta" [16,25,26]. He described these states as "non-equilibrium molecular constellations" [14,27]. Drawing insight from Albert Szent-Györgyi [28], Gurwitsch concluded that these molecular constellations must be maintained at elevated energy levels by an uninterrupted influx of energy [16,25], such that they should dissociate if the energy influx was stopped at any time [16,26]. Developing the concept further, he reasoned that because of the fundamental unity of the energetic and spatial parameters of the constellations, fluctuations due to energy migration through the molecular constellations should result in the molecules' spatial realignment [16].

It was these molecular constellations that he attributed to observations of "degradation radiation" [8,16] sudden flashes of mitogenetic radiation. Similar to emissions from rapidly-dividing cells, degradation radiation is produced by normal cells subject to a metabolic perturbation such as sudden cooling, narcosis, or cell death [29]. Studies of degradation radiation emitted from an infant rabbit during its postnatal development showed that in the early stages of development its spectra resembled spontaneous UPE from systems containing many different fluorophores. As its development progressed, the number of spectral lines decreased as the linewidths widened, until only one line remained which had no relationship to the fluorophores responsible for the original spectral lines [8].

Observations that cell mitosis could be stimulated by UV UPE under diffuse lighting conditions, but not in total darkness or bright light [1], implied that the mechanisms of UV UPE-induced mitosis in many of the organisms studied incorporated optical processes involving photon pairs, with one photon in the $\sim$ 190–330 nm wavelength spectrum and another in the visible–IR spectrum $\leq$ 1500 nm [14,16]. This claim is consistent with reports that most mitogenetic effects were induced by 190–250 nm UVC UPE in the presence of light [17,30]. However, there are very few reports of 190–250 nm UPE measurements in the modern literature to substantiate the numerous observations made using biological detectors prior to the 1950s [20]. Nevertheless, the literature supports a theory of Gurwitsch's mitogenetic effect in which biochemical chain reactions are triggered by multi-photon resonant excitations in receiver cells.

Gurwitsch's hypothesis that biological processes might rely on multi-photon effects was corroborated by reports of optical frequency doubling in liver extracts exposed to bright monochromatic light [8,14]. Frequency doubling is a non-linear optical effect mediated by an anisotropic material with non-linear susceptibility [31,32]. The effect, known as second-harmonic generation [33], involves two photons with the same frequency combining additively to form a single photon with twice the frequency (and energy) of either of the two original photons. Since Gurwitsch's pioneering work last century—decades before the first dedicated investigations of photon upconversion in the 1960s [34]—frequency doubling has been observed in various forms of biological matter [35].

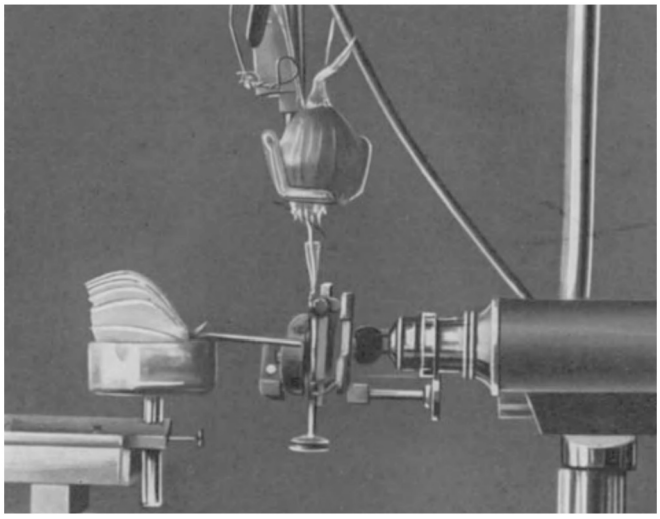

Fig. 1. Photography of Gurwitsch's onion experiment showing the emitter onion held in the inductor (a bowl to hold the inducing onion bulb, left), the receiver onion (in a frame to hold the induced bulb, top), and location of mitotic induction (center). The inductor stand is designed to allow the inducing bulb to be adjusted precisely in all directions. Reprinted from *Das Problem der Zellteilung physiologisch betrachtet* [36].

In fact, many common biological molecules such as collagen, myosin, and tubulin exhibit second-order non-linear susceptibilities [37]. Gurwitsch noted a key role for dicarbonic acids—namely glutamic acid (Glu) and aspartic acid (Asp)—in UV light-induced protein synthesis, suggesting a photochemical function for excited carbonyl pairs [14,38]. Photon upconversion is often achieved in organic systems through bimolecular processes involving chromophore pairs (*e.g.*, cooperative energy pooling [34] or triplet-triplet annihilation [39]). Modern experiments have demonstrated photon upconversion by second- and third-order harmonic generation with efficiencies consistent with observed UPE intensities [35,40]. These non-linear optical effects are now established so thoroughly in biology that they provide the basis for common biophysics experiments used in polarity measurements [41], cell cycle imaging [42], and biomedical applications [43].

Despite the foresight of his ideas, Gurwitsch's theory of mitogenetic radiation did not attain wide acceptance in his lifetime [14]. Rather, it remains a subject of broad skepticism today [8,30]. This may be due in part to the lack of dedicated experimental tests of UV UPE effects in the 190–290 nm range using modern methods, as well as the outstanding need to explain his far-reaching ideas using modern theory [1,20]. Essential difficulties associated with carrying out mitogenetic radiation experiments pertain to the ultra-low intensity of the radiation itself. Although a significant fraction of cellular UPE is in the visible spectrum, it is not visible to the naked eye, nor is it captured by common optical detectors [44].

2. Scientific background

In Gurwitsch's theory, mitogenetic radiation in the form of UV UPE from emitter cells provides an electromagnetic impulse that induces a metabolic chain reaction that stimulates cell replication in receiver cells [14]. Although electromagnetic signaling between cells is possible in principle [2,30], photonic cell-to-cell communication is limited by the low light intensity of UPE, suggesting an adverse signal-to-noise ratio S/N where S and N are the respective intensities of the signal and the ambient noise [30]. The low intensity of the UV signal thus requires a detection mechanism that can discriminate and amplify the signal beyond the level of electromagnetic noise.

Although the signal-to-noise ratio of UPE to ambient light may be low under typical physiological conditions, the intensity of the UV–

visible spectrum of UPE is still several magnitudes larger than that of the electromagnetic radiation due to the thermal noise that is predicted by Planck's radiation law at room temperature [45–47]. According to Planck's law [48], the spectral intensity I per unit wavelength λ from a thermal light source illuminating the inner surface of a sphere is

$$\mathcal{L}(\lambda, T) = \frac{dI}{d\lambda} = \frac{8\pi hc^2}{\lambda^5} \frac{1}{\exp(\frac{hc}{\lambda k_B T}) - 1}, \quad (1)$$

where h is Planck's constant, k_B is Boltzmann's constant, c is the speed of light, and T is the temperature of the radiant object. At modest temperatures near $T \approx 300\,\mathrm{K}$, this corresponds to a total thermal intensity of $I_{300K} \approx 10^{-23}$ W/cm^2 over the 380–780 nm range, about five orders of magnitude weaker than UPE intensities of $I_{UPE} \approx 10^{-18}$ W/cm^2 [3].

Moreover, only the UVB and UVC parts of UPE spectra are claimed to induce mitosis, with UVC in the 190–250 nm range being considered the most significant. *In vacuo*, 157 nm UV light has been found to induce peptide condensation [49]. Similar condensation may also be induced using substantially longer wavelengths (*i.e.*, lower photon energies) under the more biologically agreeable conditions found in solution at room temperature. Significant mitogenetic effects were not reported by Gurwitsch or others using light in the UVA range beyond ~ 326 nm (which is not substantially blocked by window glass [50]). Atmospheric oxygen and ozone completely block UVC light from reaching the Earth's surface [51], and normal glass is opaque to UVB and UVC light, but glass is transparent to most UVA light in the 320–400 nm range which did not stimulate mitosis [52]. These details corroborate the finding that mitogenetic radiation was blocked by the presence of a thin (~ 0.3 mm) glass slide placed between emitter and receiver cells, but was transmitted by fine quartz [1,8,17,27].

Motivated by the sheer number of reports supporting the existence of optical signaling between cells, as well as the promising biophysical implications of them, Kučera and Cifra performed a theoretical analysis to assess the feasibility of electromagnetic communication by photon reception between cells without pronounced bioluminescent abilities [30]. Their analysis sparked a spirited debate, eliciting a counter-analysis from Volodyaev and Beloussov claiming that Kučera and Cifra's assessment of the biological feasibility of photon-based communication was unreasonably severe [1]. However, Kučera and Cifra did acknowledge that non-linear amplification of the UV UPE signal could not be ruled out [30], and all of those four authors did agree upon a narrow range of circumstances under which optical communication between cells might be feasible [1] based on the following limitations:

- It is not observed in full daylight.
- It is not observed over long distances.
- It works only as a trigger for previously prepared processes, without transferring long messages.
- It must utilize a spectral range with significantly lower background noise than UVA/visible spectra.

Kučera and Cifra specifically considered a number of possible detection mechanisms in their analysis to identify conditions under which the mitogenetic effect could be considered plausible [30]. In that analysis, they highlighted potential problems with resonant amplification due to the temporal variations in natural light [30,53]. This restriction corroborates the body of evidence for UV UPE-induced mitosis which is only documented in specific light conditions [1]. In most studies, mitogenetic effects were maximized in diffuse daylight, but were not observed in complete darkness or in bright daylight [1]. If one considers the intensity of UPE under overcast daylight conditions (1000 lux [54]) without UV filtering, the signal-to-noise ratio is as little as $S/N = 10^{-13}$ [30].

Kučera and Cifra based their analysis on coding theory using the Shannon–Hartley theorem, which predicts the maximum rate of information transfer over a continuous analog communication channel of fixed bandwidth in the presence of Gaussian noise [30]. By applying classical information theory, they presumed to rule out practically all mechanisms of UV UPE-induced mitosis based on transmissions of continuous electromagnetic waves without spectral selectivity, further reinforcing Gurwitsch's conclusion that UV UPE-induced mitosis results from a non-classical resonance effect [14,27].

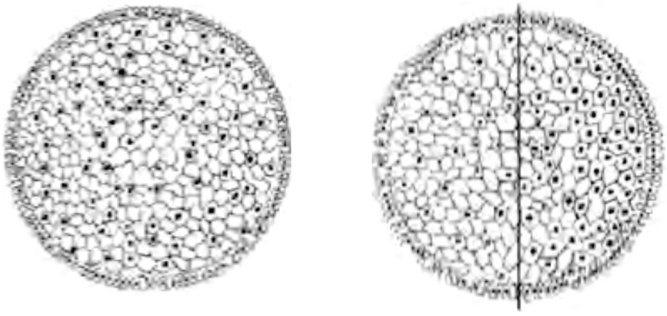

Fig. 2. Drawings of meristem cross-sections of non-irradiated (left) and irradiated (right) onion roots. The line divides the induced root into opposite halves. Reprinted from Ref. [15].

Coding theory gives the capacity C of a noisy communication channel to be $C = B \log_2(1 + S/N)$ [55]. Assuming the same maximum bandwidth of $B = 800$ THz proposed by Kučera and Cifra [30] and using $S/N = 10^{-13}$, one obtains $C \approx 100$ bits/s. If one instead considers a limited bandwidth of 250 THz (*i.e.*, the 200 to 240 nm spectral range shown in Fig. 4), then the hypothetical channel capacity becomes $C \approx 40$ bits/s. This number is not negligible, as it compares favorably to data transfer rates used to send telegraph messages early in the 1920s [56]. This result demonstrates that cellular signaling by UPE is entirely plausible, even when UV-filtering by window glass and ozone are neglected and the UV-spectral selectivity of the mitogenetic effect is entirely ignored.

To measure the intensity of UV UPE from living cells, Gurwitsch and colleagues used modified Geiger-Müller counters with photocathodes having a maximum light sensitivity in the 190–280 nm range [16]. These dedicated UV detectors were designed to be practically insensitive to visible light in order to characterize UV emissions from typical cell preparations (such as frog eggs or electrified nerve/muscle cells). UV intensities from active cells were measured in the range of 10–10^4 photons/s·cm^2 [8,16]. By filtering those photon emissions through a spectral prism, Gurwitsch and his colleagues claimed to produce narrow-band biological photon sources with intensities on the order of a single photon/s·cm^2, which were observed to induce mitosis in selected receiver cells [8,16,57]. Using those putative individual photon sources in subsequent experiments, individual photons with wavelengths up to 280 nm were inferred to provide the minimum energy required to induce mitosis in yeast receiver cells [16,18].

From those observations, it was concluded that mitosis-enhancing metabolic chain reactions could be induced in yeast cultures [16]: either by one UV photon with a wavelength of at most 280 nm in darkness, or by a UV photon of wavelength of no more than 326 nm in the presence of visible-IR light. Reproducing mitogenetic radiation effects depended critically on the preparation of the emitter and receiver systems, which were believed to reflect the underlying enzymatic chemistry of the photochemical reactions involved [16]. Likewise, these results depended critically on the correct preparation of the emitter and receiver systems [1]. For example, although some observations of mitogenetic radiation were performed in total darkness, many emitter cells released mitogenetic radiation only when illuminated with visible light [8]. Similarly, yeast was reported to work well as a UV UPE detector only when co-illuminated with non-UV light [18].

The use of Geiger-Müller counters was hence supplemented with yeast culture "biological detectors" based on UV-sensitive variations in yeast-culture growth that were reputed to be extraordinarily sensitive to low UV UPE levels, but both largely-insensitive to variations in UV UPE intensity and highly labor intensive to operate [17]. By the 1950s, cellu-

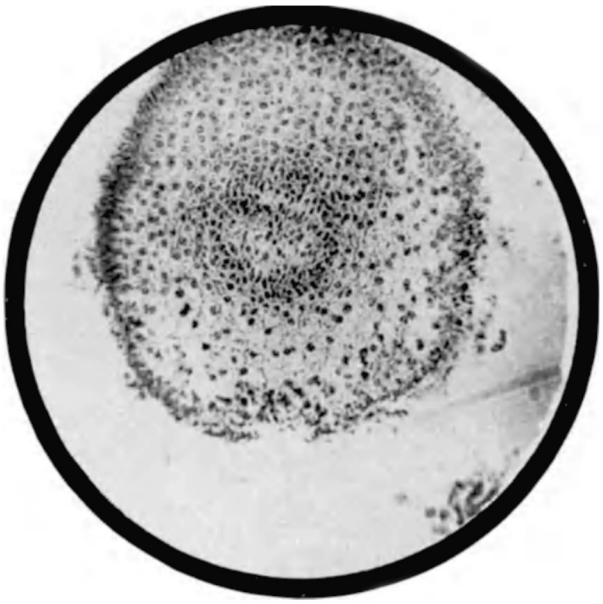

Fig. 3. Microphotograph of a root cross-section showing a "very strong" mitogenetic effect. The left side, turned toward the inducer, shows many more mitoses than the right side [15].

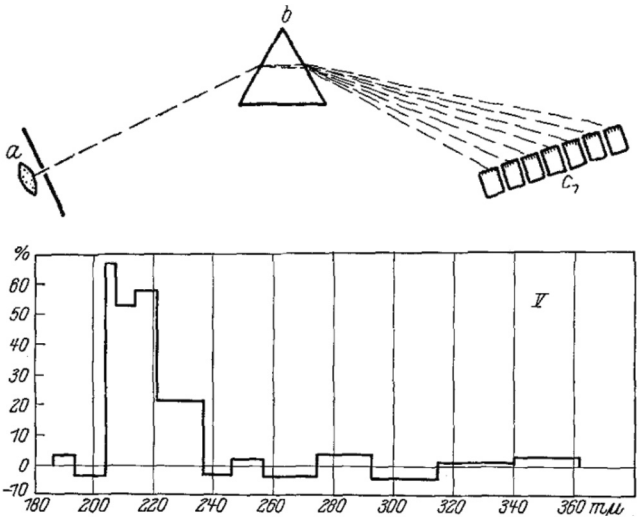

Fig. 4. Spectrograph of mitogenetic radiation from Ref. [75]: Top: Experimental arrangement indicating mitogenetic radiation source (*a*, frog sartorius), spectrograph (*b*, quartz prism), and biological detectors (c_7, yeast cultures in agar). Bottom: Sample plot of mitogenetic effect (%) obtained from the electrical stimulation of a frog sartorius muscle with respect to emission wavelength (in nm), where the effect's strength is estimated by the relative change in yeast budding.

lar UPE had been thoroughly documented using PMTs [1]. Even though cellular UPE were conclusively proven with the development of modern PMTs, those devices had much higher sensitivities in the visible range, resulting in a body of research dedicated to the study of UPE over the lower-energy 370–1270 nm range from the 1950s onward [20].

Contemporary studies of cellular UV emissions have restricted spectral bandwidth by fitting commercial PMTs with optical filters (such as in the 340 ± 5 nm range) [58], and a new generation of UV photodetectors is currently being developed with higher precision, lower energy consumption, and improved miniaturization [59,60]. State-of-the-art UV photodetector devices incorporate various designs such as semiconductor thin films, one-dimensional nanostructures, and precision nanowire systems that enable high detection rates even at high temperatures [61]. Designs based on semiconductor thin films exhibit low detection efficiencies ($\sim 40\%$) due to bias-driven noise [61], but dedicated UV PMTs with high UV specificity offer a viable alternative to achieve the extreme sensitivity needed for filter-less UV UPE detection [60]. Ongoing improvements in detector materials and designs promise to overcome past difficulties with detection limitations in the 190–330 nm range, whereas advances in miniaturization may resolve issues related to detector placement in proximity to the small biological samples involved [62].

Improved detector systems may help solve outstanding questions concerning the reputed "orderliness" of mitogenetic radiation which, according to the phenomenon of degradation radiation [8,16], is proposed to be emitted from vast stores of energy maintained in non-equilibrium molecular constellations and mobilized upon perturbation of the cellular homeostatic state [8]. If mitogenetic radiation is in fact emitted in complex time-dependent patterns, then cellular recognition of the patterns themselves represents a form of selectivity that could be used to respond to mitogenetic radiation emissions even amidst substantial noise [30]. The purported temporal orderliness of mitogenetic radiation could then also facilitate its detection in the presence of ambient optical noise.

3. Biochemical assessment

Living organisms radiate weak luminescence due to endogenous reaction cascades of photochemically-active excited states of biological molecules and reactive chemical species, particularly reactive oxygen species (ROS) [10]. Gurwitsch postulated that, in addition to UPE emissions from oxidative radical recombination processes, the existence of "non-equilibrium molecular constellations" were essential for one or more absorbed photons to initiate spatially-organized chain reactions that lead to mitosis. He further posited that these non-classical biological processes constituted the principal means of generating the most elementary manifestations of cellular life [14].

Macromolecular constellations similar to those hypothesized by Gurwitsch are now known to exist in the cytoskeletal networks of living cells [63]. Unlike static textbook depictions, cells are highly complex non-equilibrium microenvironments which are constantly rearranged by the vibrant structural dynamics of mitochondria [6], microtubules [64], and nucleic acids [65–67]. Microtubules are cytoskeletal components made of the protein tubulin which exhibit "dynamic instability" in alternating phases of growth and sudden collapse [68,69]. Dynamic instability is essential to cell functions such as mitosis, morphogenesis, and motility [70]. In microtubules, hydrolysis of the energy carrier guanosine triphosphate (GTP) drives microtubule growth. So long as new GTP-bound tubulin molecules are added to the growing microtubule more quickly than GTP is hydrolyzed, microtubule growth will continue. If the rate of polymerization slows, the microtubule will begin to dissociate as GTP is used up, resulting in "catastrophic" microtubule depolymerization [63].

Orchestrated microtubule dynamics are crucial to form and direct the mitotic spindles that segregate chromosomes into two daughter cells during mitosis [71]. Microtubule networks reorganize on exposure to UV light [72], and microtubule-assembly inhibitors can quench UV fluorescence in tubulin through their interactions with the tryptophan (Trp) chromophores therein [73]. UV-induced stress triggers secondary UPE in cells [9,74], much like UPE due to chemically-induced stress [10]. Radiation-induced UV emissions from living cells have been shown to elicit responses in nearby cells [58], demonstrating that irradiated cells can in principle become secondary UV emitters in photochemical reactions involving molecular excitations as Gurwitsch hypothesized.

As a cell's size increases, diffusive transport of diatomic oxygen (O_2) across the cell membrane becomes less efficient, increasing the amount of ROS and ROS byproducts inside the cell as the rate of ROS exchange for fresh O_2 decreases. It then becomes crucial for the cell to divide or become quiescent before oxidative stress results in permanent damage or death [76]. The cell microtubule network responds to oxidative stress by promoting enzyme interactions and cytoskeletal remodeling [77,78],

consistent with findings that oxidative changes are a critical switch to control mitotic progression [79]. Observations of UPE that arise as a consequence of oxidative processes have motivated proposals for UPE applications in health assessments of oxidative stress *in vivo* [3,80], as well as UPE detection for cancer diagnostics [81,82].

Gurwitsch had originally proposed that mitogenetic radiation signaling between cells was mediated by photon receptors embedded on the cell surface based on the observation that the likelihood of mitogenesis grew proportionally with a cell's surface area [1,14]. Cellular growth receptors were subsequently discovered, notably receptor tyrosine kinases (RTKs) which activate Ras enzymes [83]. Cell division is now known to be controlled by transmembrane receptors that transmit growth-promoting signals (via growth factors) into the cell space where mitosic regulation is dominated by Ras enzymes [84]. Ras enzymes are members of the small GTPase family of proteins which regulate practically all essential cell processes in a non-linear signaling network [85] and are critical for cell differentiation, proliferation, and survival [86].

During cellular replication, Ras enzymes are activated by high-energy phosphorylation reactions at the cell surface that initiate a chemical amplification cascade involving multiple enzymes such as cyclins and cyclin-dependent protein kinases (CDKs) [84,87]. Ras amplification is regulated by key cell-cycle processes such as gene transcription, protein synthesis, and surface receptor-mediated mechanisms [84,88]. To initiate cell replication, Ras enzymes transmit proliferative signals from the cell membrane to the nucleus and cytoskeleton [88,89].

Although Gurwitsch proposed that mitogenetic radiation might be detected by dedicated sense receptors located on the surface of each cell [1], more recent findings have demonstrated the existence of non-chemical (electromagnetic) signaling between organelles in the absence of the cell membrane. Bat'yanov [90], and subsequently Mould *et al.* [91], have demonstrated the existence of non-chemical light-based interactions between mitochondria in experiments reminiscent of those by Gurwitsch [36]. In response to claims that reports of electromagnetic signaling between cells may be false positives that are instead caused by volatile chemical signaling [30], robust protocols for distinguishing true electromagnetic signaling from volatile chemical transfer have now been demonstrated [92]. This issue is addressed in detail in a contemporary review on cellular UPE by Mould *et al.* [93].

All cells produce UPE during normal development and in response to environmental stress [94], as an aspect of cell defence, signaling, apoptosis, and ageing [95]. Plant seedlings exhibit a linear relationship between UPE and growth which varies among species [94] and can increase in response to growth hormones or oxidative stress [96]. Ultra high-sensitivity imaging of soybean roots confirmed Gurwitsch's finding that the UPE from root tips are more intense than UPE from other parts of the root [97].

ROS play a key role as cellular signaling molecules in plant and animal cells which respond to environmental stress by triggering a positive feedback loop known as ROS-induced ROS-release (RIRR) [98,99]. This feedback loop is likely to contribute substantially to the production of cellular UPE because of the link between ROS and many photo-emissive metabolic processes [6,100]. The RIRR chain reaction is thus consistent with Gurwitsch's original ideas about a role for "secondary" mitogenetic radiation during UV UPE-induced mitosis [14]:

> "It was very important to consider that the process of stimulating mitosis with mitogenetic radiation is based on the chain reactions that could be triggered by a single photon. A study of the chain reactions became possible only because of the discovery of secondary radiation, and because of the results of studying processes in non-organized systems (homogeneous solutions) after their irradiation."

Biological UPE experiments have shown that luminescence is not observed under anaerobic growth conditions [22,101], whereas microtubules dynamic instability is enhanced by ROS-free conditions [70,102]. These findings are consistent with Gurwitsch's theory that mitosis is enhanced only by very weak oxidative stimulation, unlike more intensive stimuli (either as UV radiation or ROS) which inhibit biological processes [27]. This presents a picture of a rich biophysical network in which RIRR chain reactions do not merely produce UPE as it is currently understood, but also respond dynamically to UV UPE.

ROS play many varied and complex roles in eukaryotic cell signaling and metabolism [98], where they are common by-products of mitochondrial function [103]. ROS concentrations vary significantly during the cell cycle and reach a peak during mitosis [104]. These mitogenic ROS accelerate cell-cycle progress as ROS-mediated enzyme reactions activate key enzymes during mitosis [79]. ROS-mediated reactions have been proposed to induce energy transfer and excitonic propagation in microtubule networks, which may either transport energy delivered by ROS as a form of cellular signaling, or dissipate energy as protection from its potentially-harmful effects [105].

Findings that UV-induced oxidative stress can trigger secondary UPE in living cells [9,74] have confirmed the presence of cellular reaction cascades that can generate a wide range of wavelengths of light during the relaxation of high-energy electronic states, depending on the chemical processes involved [95,106]. Given the significant optical nonlinearities exhibited by biological matter [37], photon upconversion and other higher-order resonant effects may be able to induce onset and progression of mitosis in cells that are biochemically-poised for replication [79,107].

4. Non-linear optical analysis

Although UV light is generally very hazardous to life, highly-attenuated artificial UV light in the 190–280 nm range were also noted for their capacity to stimulate cell mitosis [16,18,20]. Most of Gurwitsch's experiments were performed in diffuse daylight (*i.e.*, overcast light, about 1000 lux [54]) which was found to produce superior experimental results [1]. Experimenters were not generally concerned with the presence of ambient UV light in the laboratory (because atmospheric oxygen and window glass extinguish the relevant UV component of sunlight) [18], but care was taken to avoid the use of artificial UV sources such as open flames, spark discharges, and mercury lamps which could confound experiments [14,17].

To rationalize the impact of UV photons on cellular metabolism, Gurwitsch hypothesized that peptide synthesis could be induced by a single 270 nm-wavelength photon, or one UV photon of wavelength $\leq$ 326 nm with a second photon of at most 1500 nm, proposing that this initiated homolytic bond-cleavage reactions [8,14]. This is because amino acid polycondensation requires cleavage of a hydrogen (H) atom from the amino (NH_2) group and a hydroxyl (OH) from the carboxyl (COOH) group of peptides R and R′ to produce water (H_2O):

$$R\text{–}COOH + NH_2\text{–}R' \longrightarrow R\text{–}CO\text{–}NH\text{–}R' + H_2O.$$

A range of photochemical models were suggested after Gurwitsch offered the preliminary proposal that faint UV light could stimulate protein synthesis, based on different reactions (glycolysis, hydrolysis, proteolysis, nucleolysis, *etc.*) involving glycin, urease, carbonyls and oxygen biradicals, and various other free radicals [8,16].

Nevertheless, rationalizing Gurwitsch's mitogenetic effect as a second-order optical process is not straightforward because his research was carried out decades before the invention of the laser in 1960 [108]. Non-linear optical effects like those Gurwitsch claimed to have observed are typically assumed to require high optical intensities enabled by coherent light [35,40], unlike the incoherent light sources available in his time. However, contrary to popular reports [32], second-harmonic generation (SHG) by incoherent light has been established for almost as long as SHG using lasers, with incoherent SHG conversion efficiencies reported in the range between 10^{-11} and 10^{-14} [109]. Still, low upconversion efficiencies make SHG processes unlikely to enable cellular

weak-signal detection, assuming comparable SHG efficiencies without large enhancements.

The problem of proposing a viable theory of UV UPE-enhanced mitosis based on Gurwitsch's ideas has been further complicated by the fact that, as recently as 2011, there was still no established theory of incoherent photon upconversion [110]. Only as recently as 2020 was a statistical model of SHG by low-coherence light formally developed [109]. That alone would be sufficient to delay the development of Gurwitsch's ideas for decades after his time, because no theory of non-linear optical effects using incoherent light sources had been formulated.

However, a more fundamental problem for photon upconversion arises from the UV absorbance of the cellular matrix [16]. Although water is essentially transparent to UV light in the 190–290 nm spectral range, the presence of dissolved minerals or other molecules can substantially increase its UV absorbance [111,112]. This poses a more fundamental challenge to the concept of UV UPE-induced mitosis being enabled by two-photon upconversion: the very medium proposed to carry out the upconversion process is highly absorptive over UV-range wavelengths [47].

Gurwitsch addressed this issue by proposing that a cell which absorbed a UV photon became a "secondary radiation emitter" if it did not enter into mitosis itself [16]. Rather than transmitting photons directly, intermediate cells were proposed to "multiply" incoming photons in branching chain reactions which were later demonstrated experimentally [16,38,57]. In that picture, problems associated with high photon-absorption rates in the cellular matrix were proposed to be overcome by the transmission of mitogenetic radiation by secondary radiation emissions due to photochemical branching reactions that emit photons in quantities larger than initially absorbed [16,18]. Secondary mitogenetic emissions were postulated to arise as a consequence of energy migration along constellations of photoactive molecules which enabled the upconversion (*i.e.*, "summation of quanta") of photon energies [25,26].

Gurwitsch proposed that both the problems of high absorptivity and low upconversion efficiencies of biological matter could be overcome via the cooperative pooling of photon energies by out-of-equilibrium molecular constellations in an effect that also rationalized observations of sudden bursts of "degradation radiation" by living cells subject to significant physiological stimulus or stress [16]. Thus, it should come as no surprise that photon upconversion by cooperative energy pooling (CEP) using organic molecules has now been demonstrated to overcome problems associated with large energy losses and low conversion efficiencies of non-linear systems [34,113]. CEP enables photon upconversion with greater efficiencies and lower intensities without the need for the exotic materials of other methods (*e.g.*, based on Förster theory [114]).

During CEP, electronic excitation can be achieved either by photon absorption or by some chemical reaction such as charge-carrier recombination [113]. In a polychromophoric system with coherently-interacting chromophores, the excited energy pool may be shared between multiple chromophores. Microtubules make likely candidate systems of this kind because they have been shown to exhibit vibrant electronic properties [115] which include the experimental signatures of quantum coherent energy transfer [105,116] and coherent photon emissions [117]. Similar to CEP processes found in chromophore-laden organic thin films, coherent quantum effects have been proposed to arise in microtubules due to their intrinsic aromatic networks which are likened to optical cavities [118,119] and metamaterials [120,121].

Reported observations of degradational UPE, synchronized UPE patterns, and non-linear UPE effects corroborate evidence that the production of cellular UPE is not limited to photochemical reactions involving free radicals, but may also arise from complex out-of-equilibrium collective processes of the cell [122]. Advances in quantum optics have culminated in methods for generating non-linear optical effects using individual photons [32]. These are epitomized by "ultrastrong" interactions between light and matter [123], where electronic and photonic modes of a system act as a single entity [124]. Ultrastrong light-matter interactions have been demonstrated in thin films of organic chromophores that collectively interact to produce the effect of a "giant" dipole [123,125], reminiscent of similar collective photon emission effects proposed to exist in microtubule networks [117]. Numerical studies predict enhanced emissions from microtubules in specific molecular conformations [126], suggesting a link between coherent photoexcitations and conformation changes that occur during microtubule vibrations.

Numerical evidence for conformational control of quantum optical properties of microtubules are reinforced by observations of Fano resonances in the Raman spectra of tubulin and microtubules, attributed to interferences between coherent phononic and excitonic modes [120,127]. These results indicate that microtubules can generate hybrid vibrational-electronic ("vibronic") states which may enable coherent energy transfer between their vibrational and electronic modes [105]. Vibronic interactions also likely include exciton-polaron modes which have been implicated in microtubule dynamic instability [128]. Indeed, the rich electronic properties of tubulin have been proposed to support the amplification of electromagnetic dipole oscillations via excitations of delocalized electron and/or vibronic polaron modes which may promote synchronization and information processing [129].

The effect of amplifying a signal that is below the ambient noise level of the environment is known as stochastic resonance (SR) [130]. During SR, noise boosts a weak signal over a threshold, amplifying it by way of a non-linear response. Examples of SR include various physical, chemical, and biological processes that operate far from equilibrium [130], including many biochemical reactions which are intrinsic to life-sustaining processes [131].

Microtubule dynamics are exemplary of processes in biology which remain far from equilibrium through the continuous exchange of matter and energy with the environment [132]. Beyond structural and sensory-motor roles, numerical studies have indicated a propulsive function for them as well, presenting the hypothesis that chemical energy released by a rapidly disassembling microtubule can be converted into useful work needed to generate the large mechanical forces that propel chromosomes during cell replication [133]. The coupling between vibrational and excitonic modes of a depolymerizing microtubule is thus likely to channel the chemical energy being released into exciton modes to be emitted in a burst of photons [128,134], consistent with Gurwitsch's idea of radiation-emitting molecular constellations [8,14].

Observations of vibronic resonances in microtubules in solution [120] acquire significance in light of findings that, upon solvation, microtubule vibrational peaks condense to a single fundamental mode [118,135]. The resonant oscillations that govern this condensation of energy levels have been proposed to enable the microtubule water core to integrate surrounding vibrations in a noise-canceling effect that may enable control of the microtubules's underlying electro-optical properties [118]. The proposed effect of this spontaneous noise reduction is to produce a non-equilibrium phase transition that enables electromagnetic control of microtubule self-assembly [135].

Rather than acting as an unwanted source of noise, microtubule fluctuations have been linked to cellular perception [136]. For example, the microtubule cytoskeleton senses and responds to mechanical stress [137] by integrating mechanical signals to avoid mechanical conflicts during plant organ morphogenesis [138]. Even though cytoskeletal microtubule networks are known to coordinate and carry out highly complex organizational tasks during mitosis and morphogenesis, current models fail to explain even comparatively simple spontaneous-synchronization effects which govern the collective beating of active microtubules bundles [139]—let alone much more complex microtubule-organizational processes such as axon growth [140].

The Kuramoto model is a mathematical description of collective synchronization in a large set of weakly-coupled oscillators, where interactions between oscillators of different frequencies tend to drive them toward synchrony [141]. Proposed correlations between coherent excitonic and vibrational states indicate the possibility of photonic interactions between nearby microtubules in a weak-coupling effect that may form the basis for oscillatory synchronization. Collective synchro-

nization by photonic coupling between microtubule vibronic modes is consistent both with observations that microtubule vibrational peaks condense to a single mode [118], and with Gurwitsch's observation that degradation radiation emitted from cells converged into a single spectral line [8].

Synchronization is one of the most prominent properties of microtubules [118,139], particularly during microtubule polymerization as they exhibit synchronous transitions between growth and depolymerization [142,143]. Microtubule synchronization is crucial to orchestrate the process of mitosis, whereby microtubules form mitotic spindles in order to segregate chromosomes from the parent cell into daughter cells. This process occurs even in plants and other simple organisms which lack a dedicated microtubule organizing center (MTOC) in the form of a centrosome [144]. For example, during interphase, plasmodia carry out highly-synchronous intranuclear mitoses in the complete absence of morphologically-defined structures to organize this task [145], indicating that microtubules possess intrinsic self-organizing properties that are then reinforced by distinct organizing centers.

Microtubules undergoing synchronous motions bear an uncanny resemblance to Gurwitsch's "non-equilibrium molecular constellations," and are well-known to rely on energy input such as tubulin-bound GTP to maintain dynamic instability or kinesin to maintain rhythmic beating [139]. Yet, to explore this fascinating possibility, the problem must be framed in terms of open quantum systems theory to account for the continuous exchange of energy between the quantum system and its optical environment, as this ongoing energy exchange may enable living organisms to achieve significant light-matter coupling without conventional quantum optical methods to confine light [125].

Resonant phenomena are especially important to producing unconventional quantum and non-linear optical effects [32,146], which are essential to understand quantum effects in biology where conventional materials and mechanisms of quantum optics are unavailable [147]. Recent advancements in open quantum systems theory hold promise to unveil new horizons for the development of novel quantum technologies based on out-of-equilibrium effects, such as coherent mode-locking in the absence of the natural saturable absorbers, high quality factors, and substantial material non-linearities that are typically required to generate quantum optical effects [148].

5. Quantum optical theory

Living systems require the continuous influx and outflux of matter and energy to achieve homeostasis. Out-of-equilibrium dynamics are intrinsically different from those of conventional quantum mechanical models which typically assume system dynamics either to be closed or in equilibrium. More recently, quantum theory was formally extended to the domain of driven/damped systems involving gain and loss [149]. This theory is characterized by a symmetry of nature known as spacetime-reflection symmetry, or likewise "parity-time" symmetry, that rigorously accounts for open quantum systems with steady throughput. This theory extends existing models of dissipative quantum systems already used to describe such effects as electron tunneling [150], magnetic field sensing [151], and superradiance [152,153].

Introducing driving into existing models of damping in open quantum systems theory is necessary to account for the effect of mitogenetic radiation on living cells if one is to seriously consider Gurwitisch's hypothesis that the effect is enabled by "non-equilibrium molecular constellations." Moreover, open quantum systems theory is likely to be relevant to any unconventional enhancements to energy transmission and emission that would be necessary to enable these effects. As an example, photosynthetic biology has taken on an exemplary role in studies of systems exhibiting open quantum system dynamics insofar as system fluctuations can help contribute to fast and efficient light harvesting [154,155] and environmental noise is predicted to assist electron transfer to the reaction center of the photosynthetic complex [156].

Gurwitsch's proposal that UV UPE can initiate a chain reaction by way of photon absorption events in cells during mitosis implies that UV biophotons can induce photochemical resonances in cells. Effects of this kind, in which an incident particle is briefly captured as a metastable bound state before it subsequently decays, are known in quantum theory as scattering resonances [157,158]. It is therefore expected that resonant scattering theory will be needed to formulate the essential physical models and chemical reaction schemes to establish a conceptual basis for experimental tests of UV UPE-induced mitosis.

Quantum optics provide a framework to describe non-linear optical effects as quantum resonances (as anticipated by Gurwitsch [14,27]). Unlike standard non-linear optical effects that occur out of resonance [31], observations of UV UPE-induced mitosis implicate a resonant transition involving strong light-matter interactions [32]. Quantum resonances due to strong light-matter interactions can enable weak electromagnetic stimuli to produce significant material changes in systems that are poised to respond to specific changes in the environment [159].

The conventional quantum mechanical formalism preserves a property known as "Hermitian symmetry" [160] which ensures that all the states of a quantum system are preserved in time and that its dynamics under time-reversal are in fact the reverse of its dynamics running forward in time [161]. Indeterminism enters into conventional quantum theory with the measurement postulate, where time-reversal symmetry is broken only by the interaction of a quantum system with a classical measurement device. Unlike the idealized dynamics of closed Hermitian systems which allow for no external interactions except classical measurements [162], living organisms are sensitive to their environment and must stay in perpetual contact with their surroundings—gathering resources while expelling excess heat (entropy) to sustain life [163]. As a consequence, conventional quantum mechanics must be extended to account for the intrinsically open boundaries and irreversible dynamics of living organisms using "non-Hermitian" open quantum systems theory [164].

Non-Hermitian quantum theory was pioneered in studies of collisions by Born [165] and Dirac [166], and of α-particle decay by Gamow [167,168], which describe the asymptotic behavior of quanta that appear or vanish from the quantized vacuum field [165]. In quantum collision or scattering theory [157], the assumption of an isolated quantum system is relaxed to describe its scattering of quanta in characteristic incoming and outgoing waves [157,169]. Spontaneous decay processes such as fluorescence and phosphorescence constitute fundamental radiative processes of this kind. Although the closed formalism on which quantum mechanics is based breaks down in this limit [160], this failure is amended by rigging the Hilbert space with a mapping to an extended distribution [170] that restores mathematical rigor to the Dirac formulation of quantum theory [171,172]. The construction of this "rigged" Hilbert space (formally a "Gel'fand triple") allows the description of quantum mechanical states that are not bounded at infinity [173].

This formulation of quantum theory is essential to the picture of quantum resonances established in the pioneering works of Fano [174] and Feshbach [175] that extended Breit and Wigner's theory of scattering [176] following Dirac's seminal approach [166]. In Fano's model [174], a discrete stable state is "diluted" into a band of unstable states with a bandwidth given by its coupling to the continuum. Feshbach's method expands this approach to account for elastic collisions which conserve energy from the incoming wave through a resonant subsystem during its scattering to an outgoing counterpart wave [175].

Open quantum systems theory is formulated in terms of stochastic processes on a Hilbert space, where the knowledge about an open quantum system is defined by the probability density operator ρ [177]. The system represented by ρ is "open" in the sense that ρ can represent the effect of a projective measurement performed on any part of the quantum system $\mathcal{S}$ upon the observation of a subsystem $\mathcal{S}_1$ contained by $\mathcal{S}$ [177]. This is by virtue of Schmidt's decomposition [178], which requires that any quantum state $|\psi\rangle$ on a composite Hilbert space $\mathcal{S} = \mathcal{S}_1 \otimes \mathcal{S}_2$ can be written as a sum of tensor products, $|\psi\rangle = \sum_{i=1}^{m} c_i |u_i\rangle \otimes |v_i\rangle$ with

the coefficients c_i such that $\sum_{i=1}^{m} |c_i|^2 = 1$, where $|u_i\rangle \in \mathcal{S}_1$, $|v_j\rangle \in \mathcal{S}_2$, and m is the dimension of the smaller of the two spaces. When the outcome of a measurement of $\mathcal{S}_2$ is unknown, the resulting probability density of states on $\mathcal{S}_1$ is represented as the Hermitian density operator $\rho = \sum_{i=1}^{m} |c_i|^2 \, |u_i\rangle\langle u_i|$.

The partitioning of a composite system $\mathcal{S}$ into a principle subsystem $\mathcal{S}_1$ embedded in the surrounding subspace $\mathcal{S}_2$ enables one to designate the prospect of observing the scattered excitation either in the principle system $\mathcal{P}$ or in the surrounding space $\mathcal{Q}$ such that

$$\mathcal{P} + \mathcal{Q} = \mathbb{1}\,, \tag{2}$$

where the unit operator $\mathbb{1}$ identifies the totality of finding the excitation in $\mathcal{S}$. Following Feshbach's formalism [169], the projectors $\mathcal{P}$ and $\mathcal{Q}$ correspond to occupation of the excitation in either subspace $\mathcal{S}_1$ or $\mathcal{S}_2$, respectively.

For a particular Hamiltonian $\mathcal{H}$ on $\mathcal{S}$, a given eigenstate $|\psi_E\rangle$ satisfies the relation $\mathcal{H}|\psi_E\rangle = E|\psi_E\rangle$ for eigenstate energy E. In the continuum limit $\dim(\mathcal{S}_2) \to \infty$, the basis vectors $|v_j\rangle \in \mathcal{S}_2$ become non-normalizable (*i.e.*, not square integrable) and it is customary to take the projection of the total system onto the subsystem of interest, $\mathcal{P}\mathcal{H}|\psi_E\rangle = \mathcal{P}E|\psi_E\rangle$. Applying eq. (2), one obtains

$$\mathcal{P}\mathcal{H}(\mathcal{P} + \mathcal{Q})|\psi_E\rangle = E\mathcal{P}|\psi_E\rangle\,. \tag{3}$$

Likewise for $\mathcal{Q}$, one finds $\mathcal{Q}\mathcal{H}(\mathcal{P} + \mathcal{Q})|\psi_E\rangle = E\mathcal{Q}|\psi_E\rangle$ which is reduced to $\mathcal{Q}|\psi_E\rangle = (E - \mathcal{Q}\mathcal{H}\mathcal{Q})^{-1}\mathcal{Q}\mathcal{H}\mathcal{P}|\psi_E\rangle$, where $(E - \mathcal{Q}\mathcal{H}\mathcal{Q})^{-1}$ is the scattering propagator [175] and $\mathcal{Q}\mathcal{H}\mathcal{P} = (\mathcal{P}\mathcal{H}\mathcal{Q})^{\dagger}$ is the configuration interaction [174]. Inserting the expression for $\mathcal{Q}|\psi_E\rangle$ into eq. (3),

$$\left(\mathcal{P}\mathcal{H}\mathcal{P} + \mathcal{P}\mathcal{H}\mathcal{Q}\frac{\mathbb{1}}{E - \mathcal{Q}\mathcal{H}\mathcal{Q}}\mathcal{Q}\mathcal{H}\mathcal{P}\right)|\psi_E\rangle = E\mathcal{P}|\psi_E\rangle\,, \tag{4}$$

one obtains the effective Hamiltonian of subsystem $\mathcal{S}_1$:

$$\mathcal{H}_{\mathcal{P}}(E) = \mathcal{P}\mathcal{H}\mathcal{P} + \mathcal{P}\mathcal{H}\mathcal{Q}\frac{\mathbb{1}}{E - \mathcal{Q}\mathcal{H}\mathcal{Q}}\mathcal{Q}\mathcal{H}\mathcal{P}\,. \tag{5}$$

This effective non-Hermitian Hamiltonian is typically re-written in the form

$$\mathcal{H}_{\mathcal{P}}(E) = \mathcal{P}\mathcal{H}\mathcal{P} + \Delta(E) - \frac{\mathrm{i}}{2}\Gamma(E)\,, \tag{6}$$

where $\mathcal{P}\mathcal{H}\mathcal{P}$ is the Hermitian Hamiltonian of subsystem $\mathcal{S}_1$, $\Delta(E)$ denotes the resonant offset, and $\Gamma(E)$ is the resonance width for the characteristic excitation energy E. Note that the effective Hamiltonian $\mathcal{H}_{\mathcal{P}}(E)$ need not be a linear function of the scattered energy E. To the contrary, $\mathcal{H}_{\mathcal{P}}(E)$ becomes singular as $\langle\psi_E|\mathcal{Q}\mathcal{H}\mathcal{Q}|\psi_E\rangle \to E$.

The Hamiltonian (6) is characteristically non-linear and non-Hermitian [164]. It therefore does not obey certain premises of conventional quantum theory, such as the reality of its eigenspectrum or the unitarity (*i.e.*, conservation of probability) of its dynamics [179]. Nevertheless, an important class of non-Hermitian Hamiltonians exist which satisfy another property known as space-time reflection symmetry (*i.e.*, parity-time symmetry) [180]. A non-Hermitian system that conserves parity–time (PT) symmetry is identical to itself under the application of parity (spatial "mirror-symmetry" inversion) and time-reversal operations, and thus can still support a real eigenspectrum in spite of being an open quantum system [181].

PT-symmetric Hamiltonians have either "unbroken" symmetry for which the usual consequences of Hermitian symmetry are recovered [182], or broken PT symmetry for which they are not [183]. A PT-symmetric system can undergo a phase transition between its broken and unbroken phases, as the strength of its driving/damping terms are varied, at an "exceptional point" where its dimension is lowered as its eigenstates coalesce into a singularity [184]. A typical example of this is found in the effective Hamiltonian for a pair of coupled states:

$$\mathcal{H}_{\mathrm{PT}} = \begin{bmatrix} +\mathrm{i}\gamma & \kappa \\ \kappa & -\mathrm{i}\gamma \end{bmatrix}. \tag{7}$$

The Hamiltonian (7) designates a pair of coupled degenerate modes that exhibit real gain or loss proportional to $\gamma > 0$ and interact with a coupling constant $\kappa \in \mathbb{R}$. The PT symmetry of the system is unbroken for large coupling $|\kappa| > \gamma$, with a real spectrum of eigenvalues $\varepsilon = \pm\sqrt{\kappa^2 - \gamma^2}$. For weak coupling $|\kappa| < \gamma$, its spectrum takes on the imaginary eigenvalues $\varepsilon = \pm\mathrm{i}\sqrt{\gamma^2 - \kappa^2}$. As the coupling between modes is turned off ($\kappa = 0$), one degenerate mode undergoes an exponential gain ($+\gamma$) while the other undergoes the same rate of loss ($-\gamma$) [185]. At the exceptional points $\kappa = \pm\gamma$, the eigenstates of the system coalesce into the singular eigenvector $|\phi\rangle$, where $|\phi\rangle = |0\rangle + e^{-i\pi/2}|1\rangle$ is fixed in a superposition of the two basis states

$$|0\rangle = \begin{bmatrix} 1 \\ 0 \end{bmatrix}, \qquad |1\rangle = \begin{bmatrix} 0 \\ 1 \end{bmatrix}. \tag{8}$$

In non-Hermitian systems, PT-symmetry breaking coincides with the emergence of features associated with exceptional points [181], such as non-linear amplification [185], enhanced sensing [186], and "perfect" absorption [187]. Moreover, non-reciprocal energy transfer [188] can provide the means to amplify signals while protecting them from noise and undesirable feedback in a driven-dissipative photonic network (such as in a microtubule), where enhanced transmission and amplification may be achieved through judicious engineering of coherent and dissipative processes [189]. Counterintuitively, noise and loss can work synergetically in non-Hermitian resonators to accomplish signal amplification of up to three orders of magnitude based on an exceptional point-based mechanism characterized by bistable switching [185] which resembles the transitions between growth and collapse exhibited by microtubules during dynamic instability.

It is noteworthy that Gurwitsch formed his hypothesis about multiphoton excitation processes—even proposing the detection of free radicals by resonance scattering [14]—decades before the first observations of two-photon absorption and upconversion were performed in the 1960s [190,191]. His ideas also pre-dated essential theoretical concepts such as SR by half a century [130], which has prompted researchers to express the need for an explanation of Gurwitsch's theory in modern terms [20]. Non-Hermitian quantum optics provide an interpretive model to express a definitive representation of his theory.

6. Discussion

The problem of mitogenetic radiation has been called one of the most interesting in modern biology [18], and it remains one of the most challenging after more than a century of work. Hundreds of papers have been written on the topic with publications coming from biological and physical laboratories worldwide, often with prestigious international reputations [8,18]. The problem is steeped in controversy because prominent claims to refute Gurwitsch's results are countered with arguments that negative results are the consequence of poor methodologies in laboratories which were unable to reproduce the effect [8]. In return, critics have argued that Gurwitsch did not publish any clear-cut description of the necessary details for the preparation of the materials, or a sufficient evaluation of possible errors involved, and that the descriptions he did provide were often contradictory [18]. Yet this does not explain the penetrating nature of his scientific predictions or the countless successful laboratory reproductions of his research.

Although the phenomenon of UV UPE-induced mitosis was supported by hundreds of studies of Gurwitsch's findings in the first twenty years following his discovery of the effect, less than a score of negative results had a deterring effect on the research for decades to follow [1]. This is not surprising, given that most of the attempted reproductions were performed long before the development of many physical, chemical, and cytological concepts necessary to interpret the underlying processes. The absence of a theoretical framework needed to distinguish between positive and negative controls left some investigators to interpret negative control experiments as refutations of Gurwitsch's results

in a pattern which deterred subsequent studies of the mitogenetic effect for decades [1].

Difficulties with reproductions of Gurwitsch's findings from groups who did not follow his procedures have been ascribed to major violations of the methodology needed to obtain positive results [1]. Negative experimental results may therefore be attributed to failures to apply the requisite positive controls. Although some of those negative results involved only simple oversights such as the failure to document the quality of quartz glass, others involved critical methodological deviations from prescribed procedures such as the incorrect preparation of yeast cultures, inordinate UPE exposure durations, and improper observation timing [1]. These included those cases where yeast cultures prepared as receiver cells were not exposed to UPE during their lag phase, growth media were prepared at incorrect temperatures or saturation levels, UPE exposure durations were too long, or adequate time was not given for mitosis to occur between UPE exposure and histological observations [1]. A full list of the methodological deviations of negative experiments is found in Ref. [1].

Gurwitsch identified UV UPE-induced mitosis as a form of resonance effect more than eighty years ago [14], but the intervening decades passed without an attempt to formulate his resonance concept as a quantum effect [20]. Mitogenetic effects are readily interpretable in the framework of open quantum systems theory, where the most striking results involve resonance phenomena which are remarkably sensitive to experimental controls [157,192]. Controversial aspects of mitogenetic radiation gain new significance when the negative works are reinterpreted as crucial negative controls that establish the validity and reliability of the theory. For example, the need for high-quality quartz, a UV range of 190–290 nm, ageing or lag-phase yeast cultures, and characteristic time-scales associated with critical UV UPE exposure and observation times may all be taken as indications of resonance effects.

Recognizing the inherent inadequacy of classical principles to account for non-classical biological processes, Gurwitsch anticipated the need for the principles of quantum physics to interpret his findings in terms of the resonant amplification of individual photons [14,27]. Interactions between light and matter are described by principles of quantum electrodynamics [193] exemplified in the quantum theory of scattering [194,195]. The concurrent effect of damping and driving in living cells also implicates a role for open quantum system dynamics which can likewise enable signal amplification effects [161,196]. This is essentially what prompted Gurwitsch and collaborators to present the existence of mitogenetic radiation as *de facto* evidence for the non-equilibrium properties of living matter [197].

Nevertheless, the seemingly-paradoxical aspects of the problem of UV UPE-induced mitosis have left some reviewers to conclude that it is either impossible or it results from principles not known to exist in living cells [30], consistent with longstanding skepticism concerning the effects of electromagnetic fields on living tissue and the prevailing viewpoint that such effects are limited to semi-classical tissue-heating phenomena [198]. Although the net power flux of UPE from living cells is far less than that of ambient noise under typical terrestrial conditions, the conclusion that this renders UV UPE indistinguishable from noise is based on semiclassical reasoning that overlooks both the quantum nature of the absorption of UV light and the complete absence of 190–250 nm spectrum radiation in terrestrial sunlight [30]. Gurwitsch's premise that the mitogenetic effect is a result of non-classical, out-of-equilibrium resonance phenomena is dismissed almost out-of-hand, seemingly because the narrow range of mechanisms that he proposed to be capable of producing observed mitogenetic effects fell outside the broad preconceived notions of other authors [8].

In this respect, the UV UPE signaling problem of the mitogenetic effect is typical of problems in quantum biology, where classical principles are applied based on a presumption that aqueous conditions inside the cell preclude coherent excitations of collective quantum effects [134]. There is a prevailing view that the microenvironment of the cell is too "warm, wet, and noisy" to allow for significant quantum effects [199,200], despite established research demonstrating applications of quantum mechanics to numerous areas of biology including biomolecular excitations, van der Waals interactions, electron and proton tunneling, and biochemical reaction dynamics [201,202].

Preconceptions about quantum effects in biology are at odds with full quantum mechanical models which predict energy transfer dynamics of photoactive biological molecules to be governed by the multimodal nature of the surrounding vibrational environment, where the hybridization of electronic and vibrational degrees of freedom can be used to control enzyme activity by dramatically altering interactions between light and matter [203]. Far from acting like "classical" thermal reservoirs, realistic biological baths have non-trivial spectral densities which are likely to drive fluctuations in biological systems towards ordered states which accumulate coherence [204] (see also Sec. 7.2 of Ref. [205]). These states are necessary to account for the transmission and amplification of electromagnetic radiation in the form of UV UPE through biological materials filled with light-scattering molecules that absorb and dissipate high energy photons through oxidative cellular processes [47].

The revelation that a quantum system's environment can mediate quantum mechanical interactions may come as a surprise insofar as it is common to view the continuum only as a source of decoherence [164]. As such, biological decoherence estimates have assumed unitary dynamics modified only by dissipative effects of irreversible thermalization and spontaneous decay [177,206,207], unlike open quantum system dynamics in the vicinity of an exceptional point which can differ dramatically from those of conventional quantum mechanics [161,196,208].

In Gurwitsch's proposed theory of the mitogenetic effect, out-of-equilibrium molecular mechanisms enable photonic processes that resonate with incoming and outgoing radiation in the form of UV UPE and ambient light. The highly-complex phenomena underlying these effects have important consequences for the understanding of health, medicine, and the principles of living matter. Although cellular UPE have already drawn attention for their use in medical diagnostics, the implications of this work have yet to attract serious interest for use in radiation therapy, developmental biology, or tissue engineering, let alone fundamental investigations of cellular coordination and control. It is posited that Gurwitsch's model of UV UPE-induced mitosis provides a keystone effect not only for our understanding of cell cycle timing and metabolism, but a fundamental basis for interpreting a range of effects including cell regulation, regeneration, morphogenesis, cognition, and quantum control.

7. Research recommendations

Resonances are quantum effects which can enable the activation of a variety of molecular processes [192]. According to Gurwitsch's model, the absorption of UV UPE is believed to initiate mitosis by way of photo-oxidative chain reactions that are enabled by optical non-linearities and photochemical resonances in living cells [14]. Though the effect is reported to be common in living cells, it is highly sensitive to experimental conditions that are proposed to characterize the resonance processes involved. This work lays out an experimental basis to verify the quantum resonance theory of UV UPE-induced mitosis.

The mitogenetic effect was verified in several hundred works that corroborated specific criteria for it to be observed under specific conditions using a wide range of cell types [1], such as yeast cultures which could be used as receiver cells only in ageing cultures or during the lag phase of growth in fresh cultures. UV UPE induced mitosis only in yeast cells that were poised for replication or were already metabolically depleted, but not in vibrantly-replicating cultures [1]. Yeast receiver cultures that were prepared under marginal growth conditions (*i.e.*, at low temperatures and poor or oversaturated growth media) produced affirmative results, reflecting the sensitivity of the effect to the availability of surrounding resources [1].

In contrast, only cells from growing cell cultures, active muscle or nerve tissues, healthy blood, malignant tumors, or regenerating tissues were found to act as UV UPE inducers [1]. Those cells would also be expected to generate significant amounts of high-energy UPE, unlike inactive cells from stunted or slowly-growing cell cultures or energetically-depleted cells from the blood of diseased, ageing, or exhausted persons. Those energetically-depleted cells could not be used to reliably produce UV UPE-induced mitosis in other cells [1].

Experimental methods that ignored Gurwitsch's guidelines on UPE exposure times failed to reproduce mitogenetic effects when receiver cells were significantly overexposed to UPE [1]. This is to be expected according to findings that modest increases in oxidative stress can accelerate cell proliferation, but substantially-increased ROS levels lead to cell cycle arrest, apoptosis, or necrosis [76,79]. Furthermore, UV UPE-induced mitosis was not observed in the presence of ambient light from other UV sources, which would overpower the biological UPE signals [1,14]. Hence, the first and foremost experimental task must be to reproduce Gurwitsch's fundamental finding that living cells can respond to UVB and UVC spectrum light. This spectrum of light falls far outside the 350–1300 nm range in which UPE is currently well-documented. Reproductions of modern results demonstrating emissions of light from living cells in the 210–390 nm spectrum are most critical [21,22].

If these results can be replicated, then the next most crucial step is to characterize these light emissions in terms of intensity, as well as relevant metabolic and environmental correlates. Reports from Gurwitsch's time noted that yeast cultures prepared in the exponential growth phase were particularly effective UV UPE emitters when illuminated with visible light. Conclusively establishing an empirical basis for UVB/UVC range emissions from yeast (or similar) cultures with comprehensive guidelines to reproduce their effects—including all relevant details for their preparation and key environmental conditions—are crucial to further mitogenetic research. Beyond that, the next critical task is to comprehensively establish a range of UV wavelengths, intensities, and ambient co-illumination conditions that can influence cell growth in correctly-prepared cell cultures (*e.g.*, yeast cultures in marginal growth conditions [1]). Likewise, care must be taken to avoid confounds related to detector limitations, which may be overcome by the use of purpose-built detector systems that enable full panoramic photon detection around the sample with high efficiency and selectivity across the 190–350 nm wavelength range.

It is notable that cellular UV emissions are implicated with highly-exothermic radical recombination reactions [24,27] which have been modeled as open quantum systems since the 1970s [209,210]. UV UPE-induced mitosis therefore likely involves photo-activated biradical reactions very similar to those involved in biological sensing of weak magnetic fields [211]. This implicates a prototypical role for radical pair dynamics that are often indicated in quantum biology [212,213]. Thus, both the generation of UV UPE and UV UPE-induced cell mitosis should be investigated for magnetic field sensitivity, similar to the recent experimental demonstrations that cellular autofluorescence is magnetic field sensitive [214].

Given the century-old controversy surrounding Gurwitsch's theory of UV UPE-induced mitosis [1,30], there is a definitive need to reproduce both positive and negative control experiments with modern lab equipment and theory. Beyond the need to reproduce mitogenetic experiments using contemporary standards with careful controls to guard against the confounding factors laid out in Ref. [30], the open quantum systems framework proposed here indicates a program for experimental research:

- Most critically, there is a need to establish an exact quantum biochemical basis to designate the action mechanism of mitogenetic radiation on the developmental processes of living cells. Experiments with the necessary controls are needed to rule out confounding effects, including adequate detector systems in the appropriate spectral range. These must also provide insight into the biomolecules and exact chemical reactions mediating the mitogenetic effect.
- Once a confound-free experimental method is used to identify the photochemical reactants and products involved in the mitogenetic effect, a set of measurements should be performed to quantify mitogenetic radiation intensities and enhanced mitosis rates under varied UV UPE-induction conditions.
- Further experimental protocols can then be defined using eqs. (5) to (7) to test the noise limits on the resonant amplification mechanisms proposed here, including SR [129,130], radical pair dynamics [209], non-reciprocal amplification [189,215], exceptional point-based sensing [161,196], and other non-linear quantum and/or chemical effects [216,217].

The aim of this experimental approach is to identify a physical mechanism for any documented mitogenetic radiation effects, as these effects cannot be explained by established mechanisms of classical or even conventional quantum theory [30]. Although Gurwitsch proposed the mitogenetic effect to rely on the presence of quantum resonance(s) between biomolecules in the receiver cells and the surrounding electromagnetic field many decades ago [14], his theoretical model was not taken up as a formal hypothesis to be investigated within the framework of open quantum systems theory. This presents a major opportunity to develop Gurwitsch's idea according to the emerging principles of open quantum systems biology.

8. Summary and outlook

During metabolism, most living cells emit radiation with photon flux densities of 1000 quanta/s·cm^2 or less [1,20], but UPE light intensities can approach 10^4 quanta/s·cm^2 in replicating or highly-stimulated cells [8,16]. Although cellular signaling via UPE is well-documented, critics have argued that if it exists as a general physiological effect, then it must employ mechanisms that are not yet understood to exist in living cells according to accepted biophysical models [30]. They claim that the photonic interactions implicated in the mitogenetic effect would be limited to special circumstances involving physical mechanisms as of yet unknown to biology [30]. This argument strongly reinforces Gurwitsch's proposal that UV UPE-induced mitoses are enabled by non-classical mechanisms (far beyond the biophysical concepts and methods available in the mid 20th century) and his claim that "structured processes" constitute the most fundamental aspect of living matter [16].

Although the concept of mitogenetic effects as non-classical resonances was proposed by Gurwitsch decades ago [14], it had not been developed according to the quantum theory of resonances [20]. Following on Gurwitsch's insights, "mitogenetic" radiation in the form of UV UPE are proposed to play a physiological role in cell replication according to open quantum systems theory [164]. UV UPE are believed to induce mitosis in resource-limited cells that are poised to replicate and hence receptive to weak stimulus. Critical assessments claiming that UV UPE-induced mitosis is implausible (because of low signal-to-noise ratios) are based on classical arguments which fail to account for the spectral selectivity of the processes in question. These arguments overlook the fact that mitogenetic radiation is hypothesized to be limited to UVB/UVC wavelengths where interference due to electromagnetic noise is minimal, unlike modern observations of cellular UPE in the UVA-visible-IR range where electromagnetic noise can be substantial.

Experimental findings indicating that UV UPE-induced mitosis is mediated by photo-oxidative processes are consistent with contemporary findings that mild oxidative stress can promote mitosis in living cells [79] in a reaction cascade that is likely linked to RIRR, Ras amplification, and the release of secondary UPE from those cells. These chain reactions may be aided by non-linear optical processes such as photon upconversion during SR amplification of UV signals by visible and/or infrared light, and likely involve non-linear chemical chain reactions as well [217]. These processes may be further amplified by a complex

photochemical network that interfaces with the cytoskeleton, where out-of-equilibrium phenomena exhibited by microtubules may play a key role in enabling signal enhancement through open quantum system effects that intensify light-matter interactions.

Living cells define prototypical open quantum systems where quantum dynamics of photobiochemical processes such as those involved in generating UPE provide key opportunities not only for investigations in quantum biology and cellular physiology, but also for fundamental physics applications [156,218]. Interpreting biological and biochemical experiments according to open quantum systems theory can lead to novel hypotheses and experimental proposals, with the promise to revolutionize our understanding of the mechanisms that govern biochemical processes in living cells. In this case, the application of open quantum systems theory enables a viable theoretical interpretation of Gurwitsch's observations of UV UPE-induced mitosis, as a potential solution to the hundred-year old mystery of the mitogenetic effect.

CRediT authorship contribution statement

Nathan S. Babcock: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The author declares no competing financial interest.

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