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FELICE DI LAUDO, LEONARDO MORINI
LUCA REGAZZI, MARTINA TOMIROTTI

ASTRAZIONI STENOGRAFICHE II

CONCETTI CHIAVE PER VIVERE CONSAPEVOLMENTE LA NOSTRA SOCIETÀ

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ASTRAZIONI STENOGRAFICHE

II

SUPERVISIONE
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SOMMARIO

PREFAZIONE

Cosa sono le Astrazioni Stenografiche? L'idea per questa collana di divulgazione scientifica prende spunto da alcune osservazioni fatte da James Flynn, il noto psicologo dell'intelligenza, famoso per l'effetto che porta il suo nome. Per Flynn, ci sono alcuni elementi culturali che, a discapito dell'importanza, possono non intersecare il cammino scolastico di tutti. Ecco quindi che sarebbe importante poter accedere a queste pillole di sapere, per poter essere cittadini più consapevoli e partecipi della vita di una società avanzata.

Per questo motivo, è nato *Astrazioni Stenografiche*, che ora giunge alla seconda edizione, con la speranza di fornire concetti nuovi a cittadini nuovi.

L'edizione di quest'anno, sempre basata su scritti degli studenti del Collegio Superiore dell'Università di Bologna, ci consente di portare nuove ed interessanti astrazioni: esploreremo il profondo rapporto che lega cervello e musica, la biologia sintetica e le sue speranze, la cosiddetta Global Health e i modi in cui viene declinata dalla nostra società, ed infine faremo il punto sulla ricerca dell'immortalità, aspirazione a cui l'umanità si è dedicata fin dalla percezione della propria limitatezza temporale.

Ci auguriamo quindi che la nostra aspirazione a formare una sempre più consapevole partecipazione alla vita della nostra specie, specialmente in questa sua fase di rapido sviluppo e cambiamenti. La paura del futuro nasce infatti dall'ignoranza del presente.

Beatrice Fraboni
Direttrice del Collegio Superiore

Matteo Cerri
Curatore della collana

LA MENTE MUSICALE

FELICE DI LAUDO

Cosa accade alla mente quando si ascolta della musica? In che modo essa viene percepita e che aspetti il cervello è in grado di cogliere, consciamente o inconsciamente, da una melodia? Quanto impatta la pratica musicale sulla formazione e sulla salute delle strutture del sistema nervoso umano?
Negli ultimi anni, gli effetti della musica sulla mente umana stanno emergendo come argomento di studio sentito in ambito neuroscientifico. Le implicazioni sul neurosviluppo e sulla prevenzione del decadimento cognitivo età-correlato attraggono l'interesse dei ricercatori: la facile modalità di assunzione e la mancanza di effetti collaterali rendono infatti l'ascolto e la pratica musicale un potenziale "farmaco" ideale.
In questo capitolo, verranno introdotti dapprima i principali attori della percezione musicale, immaginando di seguire il viaggio di una nota dalle corde di uno strumento fino ai centri superiori della mente, considerando anche alcuni casi limite come l'orecchio assoluto e l'amusia. Verranno poi presentati alcuni concetti di armonia musicale e riferimenti alle emozioni differenti che gli accordi possono suscitare e al legame tra musica e memoria. Infine, alcuni effetti positivi che la musica può avere dai più giovani ai più anziani, sottolineando alcune differenze tra il cervello di chi la pratica e quello di chi non lo fa.

What happens to the mind while listening to music? How is it perceived and what aspects is the brain able to grasp, consciously or unconsciously, from a melody? How does musical practice affect the development and the health of the human nervous system?
In recent years, the effects of music on the human mind are emerging as a new topic in the neuroscientific field. The implications on neurodevelopment and on the prevention of age-related cognitive decay attract the interest of researchers: the modality of intake and the lack of side effects make listening and practice music an ideal "drug".
In this chapter, firstly the main actors of musical perception will be introduced, imagining to follow the journey of a note from the strings of an instrument to the higher centers of the brain, also considering some extreme cases such as the absolute ear and the amusia. Then some concepts of musical harmony and references to the different emotions that chords can evoke and the link between music and memory. Finally, some positive effects that music can have from younger to older people, pointing out some differences between the brain of those who practice music and those who do not.

PREFAZIONE

Ci sono pochi settori della nostra vita che non saranno toccati dalle neuroscienze. Le domande più profonde dell'essere umano, in fondo, riguardano proprio l'essere umano stesso. La relativamente recente comparsa della coscienza ha donato ad ogni individuo della nostra specie la possibilità dell'introspezione. In questo processo, che ci porta a sentire quella vocina interiore che ci accompagna durante la giornata, la realtà intorno a noi può prendere una forma diversa da quella puramente fisica che la costituisce.

Ecco allora che un'onda può diventare un suono. E un suono può diventare musica. Quest'ultima, è importante sottolineare, non è un oggetto identificabile e descrivibile nel regno della fisica: esiste solo all'interno di quel mondo a cui la coscienza ci ha dato accesso, e che le neuroscienze cercano di comprendere.

In questo capitolo, ci troveremo quindi a seguire qual è il percorso che la fisica fa per diventare musica, un cammino ancora pieno di insoluti, ma che non farà che aggiungere un senso di meraviglia, per la complessità del nostro sistema nervoso centrale, alla meraviglia che nasce in noi all'apparire della musica. Oscar Wilde diceva che una rosa, osservata al microscopio, perde il suo fascino di rosa. Non sono d'accordo. Anzi, al contrario, la conoscenza dei meccanismi della bellezza non può che amplificare ed arricchire la nostra esperienza estetica.

Così, la prossima volta che ascoltate della musica, dedicate al vostro cervello un momento di attenzione, apprezzando l'immenso lavoro che sta facendo per far emergere quel piacere che solo in lui può essere creato.

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INTRODUZIONE

Cinque minuti al primo brano.

Sul palco è già tutto pronto per il concerto: le luci, gli amplificatori, i microfoni sono già in posizione. Il pubblico in sala chiacchiera, dai tavoli si leva una melodia confusa – è impossibile cogliere anche uno solo di quei discorsi da dietro le quinte.

Il batterista è il primo a salire sul palco. Si siede alle percussioni e dopo un cenno al pubblico comincia ad improvvisare qualcosa di leggero e al contempo deciso. Sta cominciando.

Tra i colpi dei Tom si insinua qualche nota: l'ha raggiunto sul palco il bassista col suo inseparabile strumento elettrico. I due giocano a rincorrersi per un po'.

Mi Si Sol Re La Mi. Dietro le quinte il chitarrista è alle prese con l'accordatura. «I chitarristi passano metà della loro vita ad accordare la loro chitarra, e l'altra metà a suonare con la chitarra scordata» (Fareed Haque, battuta geniale durante un live). Ecco, tira giù un accordo liberatorio ed entra di diritto alla festa, sul palco.

Il pianista lo segue un paio di metri indietro, niente in mano da roteare, niente al collo da accordare: lo sguardo verso la sala poi verso il piano. Seduto al pianoforte quegli ottantotto tasti bianchi e neri non gli sembrano poi così tanti. «Tu sei infinito, e dentro quei tasti, infinita è la musica che puoi fare»[1]. A poco a poco si inserisce nell'armonia del brano di apertura, seguendo la ritmica sempre più sincopata di basso e batteria e gli accordi di settima della chitarra.

Da quel tappeto di note, il suono del sax tenore emerge quasi naturalmente, come se ci fosse sempre stato ma fosse impossibile dare la sua opinione senza che prima ciascuno strumento avesse detto la propria.

Una breve pausa, tutti in silenzio – e non è anche questo, forse, musica? – e qualche applauso prima di iniziare. Come la luce che passa in un complesso sistema di lenti per poter osservare più da vicino gli anelli di Saturno o l'aspetto di un piccolo batterio, i loro sguardi si incrociano prima di cominciare e viaggiano, dalla batteria al basso alla chitarra al piano al sassofono.

Uno. Due. Tre. Quattro.

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[1] A. Baricco, *Novecento, Un monologo*, Milano, Feltrinelli, 1994.

I. DAL SUONO ALLA NOTA

I.1 UN RECETTORE PER IL SUONO

Immaginiamo di scendere dal palco e guardare più da vicino il pubblico, così vicino da portarci – metaforicamente – "dentro" il cervello di ciascuno spettatore. Da dove nasce la percezione musicale?

Ogni lungo viaggio deve pur cominciare con un passo e il primo passo in questo caso specifico è l'onda sonora. Ma da subito occorre complicare un po' la situazione: non tutte le onde sono uguali. Anche se in aria l'onda sonora si propaga a più di 300 metri al secondo, l'essere umano è in grado di distinguerne il timbro, ovvero la differenza – a parità di frequenza – tra sorgenti del suono. Persino un orecchio inesperto distinguerebbe un Si bemolle suonato da un violino da quello suonato da un flauto o da quello di un pianoforte, nonostante esso abbia la stessa altezza e la stessa intensità in tutti e tre i casi (ben pochi, tuttavia, riuscirebbero a nominare esattamente la nota suonata, ma ci sarà spazio più avanti per parlarne).

Dopo aver scoperto che diversi strumenti emettono suoni con diversi timbri, occorre comprendere come queste rapide differenze pressorie dell'aria, propagate fino alle ultime file di spettatori, si trasformino in note musicali. Già nel XVIII secolo si conosceva la complessa anatomia dell'orecchio, che dietro al ben visibile padiglione auricolare nasconde l'organo vero e proprio dell'udito, incastrato all'interno dell'osso temporale del cranio. Tra questi due estremi, che vengono chiamati orecchio esterno (padiglione auricolare e condotto uditivo) e orecchio interno (coclea), vi è un ingegnoso sistema di leve che dalla membrana del timpano agisce come un vero e proprio pistone: sono i tre ossicini più piccoli del corpo umano, martello incudine e staffa. La vibrazione sonora sulla membrana del timpano fa muovere la staffa che spinge contro il liquido contenuto nella coclea.

È il 1851 quando il fisiologo italiano Alfonso Corti scopre la struttura sensoriale alla base dell'udito[2]. L'organo del Corti è formato da circa 16.000 cellule "ciliate" (chiamate così perché sembrano delle microscopiche setole) che rispondono ai movimenti del liquido nella coclea piegando quelle setole: se si piegano abbastanza, la cellula genera un impulso elettrico che viene condotto al cervello e lì elaborato.

Come si distingue un suono acuto da uno più grave? Il sistema liquido-cellule ciliate è avvolto su sé stesso per due giri e mezzo (il nome coclea deriva da questa

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[2] A. Corti, *Recherches sur l'organe de l'ouie des mammiféres*, Leipzig, Verlag von Wilhelm Engelmann, 1851.

forma "a spirale"), ma immaginando di srotolare questa chiocciola si osserverà un segmento che va da una base ad un apice, che – a causa di differenze progressive nella loro struttura – "sentono" frequenze diverse. Per semplificare ulteriormente questo concetto, si può immaginare l'organo del Corti come la tastiera di un pianoforte che trasforma le diverse frequenze di onde (tasti premuti dal pianista) in diversi segnali al cervello (note musicali). Questa organizzazione, definita "tonotopica" dai neuroscienziati, viene mantenuta lungo tutto il percorso verso il centro primario dell'udito nel cervello e permette di distinguere oltre 1400 diversi suoni all'interno di un ampio range di frequenze, da 20 a 20.000 Hz (Hertz, unità di misura della frequenza).

Quindi, dal palco il suono propagato dai diversi strumenti è stato convogliato dal padiglione auricolare lungo il condotto uditivo, trasmesso dal timpano al liquido dentro la coclea e rilevato dalle cellule ciliate dell'organo del Corti: quanti nomi in così pochi centimetri.

Una conclusione importante che si può già trarre riguarda l'importanza di salvaguardare l'organo del Corti: le cellule ciliate perse non vengono sostituite e sebbene siano ben protette da insulti "meccanici" (si trovano all'interno della porzione ossea più compatta del corpo e immerse in un liquido che assorbe le vibrazioni), possono essere danneggiate da rumori intensi, persino dal volume eccessivamente alto nelle cuffiette quando si ascolta musica dai cellulari o tablet, oltre che dall'avanzare dell'età.

I.2 LE VIE CENTRALI DELL'UDITO

L'impulso è partito, il silenzio sta per rompersi. In effetti lo spettatore non ha ancora avvertito alcun suono, lo stimolo non ha ancora raggiunto la corteccia cerebrale, ma nel frattempo stanno accadendo diverse cose interessanti a sua insaputa.

Il nervo acustico è la struttura che porta l'impulso dall'organo del Corti fino alla porzione da un punto di vista evolutivo più antica (e anatomicamente più bassa) del nostro cervello: il tronco encefalico. Come qualsiasi altro nervo del corpo umano, l'acustico può essere assimilato ad un piccolo cavo elettrico con all'interno fasci di propaggini cellulari (gli assoni, ovvero quelle porzioni di neuroni che trasportano il segnale elettrico) circondati da una guaina isolante. È un nervo ma non fa male se irritato, piuttosto genera un fastidioso tintinnio dal lato interessato (coloro che soffrono di vertigini ne possono avere una idea, non a caso sia il nervo acustico che la coclea sono in strettissimo contatto con l'organo dell'equilibrio).

Tornando allo stimolo sonoro, è giunti il momento di salire verso la corteccia, per essere "sentito". Non è una arrampicata semplice, non occorre certo analizzare ciascuna stazione in cui si sofferma il segnale, ma da questa permanenza nel tronco encefalico si possono cogliere alcuni spunti di riflessione interessanti.

In primo luogo, ciascuna di queste stazioni conserva l'organizzazione "tonotopica" dell'organo del Corti, ma l'insieme di tutte queste ritrasmissioni del segnale comporta un forte effetto di filtro e di pulizia dello stesso. Gran parte delle elaborazioni nel sistema acustico è fatta prima di arrivare alla corteccia: si nota già una differenza, ad esempio, rispetto al sistema visivo, dove invece l'elaborazione avviene in gran parte dopo l'arrivo in corteccia (non va tralasciato il dettaglio che la corteccia visiva è molto più estesa di quella uditiva e che l'essere umano si è evoluto prediligendo la visione tra i sensi usati per esplorare l'ambiente che lo circonda).

In secondo luogo, l'orecchio destro e quello sinistro inviano impulsi separatamente al tronco encefalico, ma durante l'ascesa delle fibre nervose alla corteccia questi impulsi vengono in buona parte sdoppiati su entrambi i lati: sia a destra che a sinistra, quindi, salgono impulsi provenienti da entrambe le orecchie. Questo implica che una qualsiasi interruzione in uno solo dei due fasci non causa una sordità completa dal lato interessato (cosa che accadrebbe in caso di danno permanente all'orecchio oppure al nervo acustico), ma una semplice riduzione dell'udito.

Inoltre, l'integrazione delle informazioni provenienti dalle due orecchie permette di localizzare con discreta precisione la direzione del suono rispetto alla testa: ovviamente questo è legato alla lieve differenza di arrivo del suono alle due orecchie, prima da un lato piuttosto che dall'altro.

Infine, è interessante sottolineare che alcuni fasci "avvisano" il tronco encefalico quando il rumore ascoltato è troppo forte e vengono azionati di riflesso due piccolissimi muscoli nell'orecchio medio (che agiscono sul timpano e sulla staffa) smorzando il suono in ingresso. È come premere il pedale della sordina in un pianoforte, un meccanismo di difesa contro l'eccessivo volume del suono. Ed è tutto ancora incosciente.

Una volta superate le tortuosità del tronco encefalico, l'onda sonora – ormai divenuta impulso elettrico – sta per trasformarsi in vero e proprio suono percepito. La corteccia uditiva primaria è la prima regione della corteccia cerebrale che riceve lo stimolo uditivo. La prima, non l'unica. Tuttavia, come spesso afferma chi si occupa di cervello, il modo più interessante per spiegare il funzionamento di alcune aree cerebrali è quello di studiare dei casi limite, delle singolarità o delle mancanze di funzione.

I.3 L'ORECCHIO ASSOLUTO

L'orecchio assoluto è la capacità di distinguere correttamente l'altezza di una nota senza basarsi su altri toni di riferimento. E non soltanto note emesse da uno strumento o dal canto, ma anche semplici e comini rumori: un campanello può suonare in Sol diesis, una porta cigolare in Fa.

È una abilità affascinante, ma ancora poco compresa: le teorie sulla genesi e lo sviluppo dell'orecchio assoluto possono aiutare nella descrizione di questo viaggio della musica dal palco alla mente. Per cominciare, la maggior parte degli studi stima la frequenza di questa abilità in un soggetto ogni 10.000. La precisione dell'orecchio assoluto varia, ma in genere si riescono a distinguere oltre 70 diverse note nel range delle frequenze udibili.

Una delle prime domande che gli scienziati si sono posti è: "Ma con l'orecchio assoluto ci si nasce? Oppure lo si acquisisce con la pratica?".

La risposta, come spesso accade, sta nel mezzo: una predisposizione genetica (ci sono dei pezzetti di DNA meritevoli di studio, ma al momento è più ragionevole restare su questo termine più vago) porta a questa abilità se opportunamente stimolata. Sembra, in particolare, che quanto più precoce è l'esposizione alla musica, tanto più è probabile svilupparlo; invece, non sembra esserci alcun legame con la durata dell'esercizio musicale.

Non tutti hanno espresso un parere così drastico: David L. Burge nel 1981 pubblica un articolo su *Contemporary keyboard* in cui parla di "orecchio musicale o relativo". Qualunque musicista può raggiungere un buon livello di discriminazione tra i toni, anche se non con la precisione e la naturalezza di chi possiede l'orecchio assoluto.

Un'altra domanda molto gettonata in questo ambito di ricerca è stata: "Cosa cambia nel cervello di questi soggetti rispetto al resto della popolazione?". Prima di dare una risposta è doveroso fare una importante considerazione: se finora il percorso delle note dall'orecchio fino alla corteccia uditiva primaria è sembrato piuttosto simmetrico tra destra e sinistra del corpo, ora nei centri di elaborazione superiore il discorso cambia e si assiste ad una più o meno evidente "lateralizzazione" delle informazioni (alcuni impulsi elettrici arrivano nell'emisfero destro per attivare una specifica funzione, altri arrivano all'emisfero sinistro, altri ancora arrivano da entrambi i lati).

Gottfried Schlaug e colleghi[3] hanno dimostrato che la più importante differenza tra un cervello comune o con orecchio relativo e uno che presenta orecchio assolu-

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[3] J.P Keenan, V. Thangaraj, A.R. Halpern, G. Schlaug, *Absolute Pitch and Planum Temporale, in NeuroImage*, 2001.

to risiede in un'area vicina alla corteccia uditiva primaria, con un nome latino (ai vecchi anatomisti piacevano particolarmente le lingue classiche per ovvie ragioni), il Planum Temporale. Chi possiede l'orecchio assoluto ha il Planum Temporale sinistro più esteso che a destra; gli altri cervelli invece no, non presentano grosse differenze di lato. E quindi?

Chi studia i correlati neurali del linguaggio sa che questa struttura è una di quelle implicate nella percezione del linguaggio verbale: la musica e il linguaggio potrebbero vedere qui uno dei loro tanti punti di contatto nella anatomia del cervello.

A conferma di ciò, è vero che l'orecchio assoluto si presenta in un soggetto su 10.000, ma la maggior parte di questi proviene dall'Estremo Oriente: ecco come l'apprendere una lingua come il vietnamita o il cinese mandarino (lingue definite "tonali", in cui il significato di una parola può cambiare completamente solo per come la si pronuncia) favorisce e mantiene lo sviluppo dell'orecchio assoluto. Le lingue "non-tonali" come quelle occidentali sembrano al contrario favorire la perdita di questa innata capacità di discriminare i toni per lasciare spazio alla comprensione sintattica e grammaticale. L'ascolto della musica nei bambini molto piccoli può fungere da appiglio per l'orecchio assoluto, così da non "dimenticarlo".

1.4 L'AMUSIA

La maggior parte delle persone apprezza la musica, ma una percentuale variabile della popolazione (1,5-2%) non riesce a mostrare alcun interesse per essa. Per comprendere questa condizione, che i clinici chiamano "amusia", occorre prima dare qualche definizione.

La musica è un suono organizzato secondo principi di tono, ritmo e armonia, che si sviluppa secondo differenti timbri. Del ritmo è stato discusso nella sezione 1.1 e l'armonia sarà la protagonista della prossima sezione: non resta che definire "tono" e "ritmo", due componenti della musica che il cervello processa in differenti aree della corteccia. Procedendo con ordine: il tono è inteso qui come la traduzione del termine inglese "pitch", ovvero la posizione di un dato suono all'interno del range completo delle frequenze udibili (va infatti distinto dal significato tecnico musicale di tono come intervallo di seconda maggiore); il ritmo è una successione di accenti e pause che può o meno seguire un modello ciclico. Le definizioni sono complicate, è vero, ma se il significato della parola "ritmo" appare immediato, lo stesso non vale per il "tono", che in italiano ha molteplici sfaccettature (volume, intonazione, atteggiamento, ecc.).

Ora, lo studio dei soggetti con amusia, "mancanza della percezione musicale", ha permesso di comprendere quali porzioni cerebrali sono essenziali per elaborare toni e ritmo. Si anticipa un concetto importante: tutte queste aree sono connesse tra loro – e con molte altre aree nelle zone più disparate del cervello – quindi per godere a pieno della musica o di qualsiasi altra forma d'arte occorre una grande integrazione di informazioni. L'intento dei neuroscienziati è quello di scomporre queste informazioni fino al livello più elementare possibile e scovare le aree cerebrali che processano ognuno di questi mattoncini. È un modo, non l'unico, per approcciarsi allo studio del cervello.

Tornando all'amusia, la forma più studiata è quella "acquisita": il soggetto prima riusciva a percepire ogni aspetto della musica, poi accade qualcosa che fa perdere una o più componenti, tono o ritmo, alla musica. L'ictus purtroppo è la causa più frequente e i medici sono spesso in grado (con l'aiuto delle immagini in risonanza o TC) di identificare la zona del cervello che "muore" per mancanza di ossigeno. Si è visto che un fascio nervoso in particolare, se danneggiato, provoca più facilmente amusia: è il fascicolo fronto-occipitale inferiore, nel cui nome lungo e complicato sembra viaggiare la via nervosa più importante per la percezione integrata dello stimolo musicale. Anche stavolta viene chiamato in causa il linguaggio, che vede nell'IFOF (l'acronimo è decisamente più maneggevole) l'attore principale della fase di comprensione del parlato[4]. Ma c'è dell'altro. Alcuni soggetti dopo l'ictus non hanno problemi a riconoscere l'altezza relativa delle note che vengono fatte ascoltare, ma non riescono a distinguere due ritmi diversi di uno stesso gruppo di note: le strutture coinvolte in questo caso sono nell'emisfero sinistro e si chiamano fascicolo arcuato e uncinato. Se le stesse strutture vengono coinvolte dal lato destro, il soggetto non riesce a distinguere le differenze tra due note non troppo distanti tra loro, né è in grado di riconoscere una serie di note cambiate di tonalità (spostate tutte un po' più in alto o in basso di frequenza), ma ne distingue chiaramente il ritmo.

Come se l'emisfero sinistro fungesse da metronomo e il destro percepisse la qualità della nota. È comunque chiaro che questa approssimazione che distingue la parte logica e quella emotiva in emisferi diversi è grossolana e non tiene conto della integrazione delle informazioni di entrambi i lati, ma può risultare utile per tenere a mente alcuni punti chiave.

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[4] A.J. Sihvonev *et al.*, *Tracting the neural basis of music: Deficient structural connectivity underlying acquired amusia*, in *Cortex*, 97, 2017.

Riassumendo, dalla corteccia uditiva primaria, che ha permesso allo spettatore di sentire la nota arrivata dal palco, l'impulso si propaga nelle cortecce vicine (uditiva secondaria, giro di Heschl, Planum Temporale) e viene portato in altri lobi cerebrali (come quelli frontali) dall'IFOF, mentre passando nel fascicolo arcuato e uncinato di entrambi gli emisferi si è potuto apprezzare tono e ritmo delle note. Tralasciando tante strutture importanti, la maggior parte delle quali nel lobo temporale, il concetto che deve essere chiaro è che a questo punto la nota è identificata e messa in relazione ritmica con le altre.

Questa, grosso modo, è la base teorica della fredda percezione di una nota. Ma nessuno crede che la musica si possa ridurre a questo: le note sono tante, si sovrappongono, suscitano emozioni e ricordi. Occorre un salto concettuale.

La musica è la più libera, la più astratta, la meno vincolata tra le arti: nessuna struttura narrativa, né rappresentazione pittorica, nessun bisogno di regolarità di metro, né di limiti stretti di una cornice ostacola il funzionamento intuitivo della mente creativa.

Aaron Copland

2. DALLE NOTE ALLA MELODIA

2.1 L'ARMONIA

Armonia (dal greco *unione*, *proporzione*, *accordo*) è figlia del dio della guerra Ares e della dea dell'amore Afrodite, almeno secondo quanto racconta Esiodo nella sua famosa *Teogonia*. Guerra e amore. Armonia è sposa di Cadmo, il fondatore della città di Tebe e di quella stirpe di cui canta gran parte della Tragedia Greca.

Se poi si pensa che il primo titolo che Nietzsche aveva in mente per la sua celebre *Nascita della Tragedia* del 1871 era proprio *Il dramma musicale greco*, si può avere un'idea di quanto la musica permeava i cori della Tragedia del mondo classico, come prima aveva fatto con i cantori dell'Epica e con i poeti della Lirica. Ritmo e armonia.

Nessuno dei due implica l'altro per esistere e di certo non sono nati insieme: le prime testimonianza di musicalità sono proprio le percussioni, battere il tempo, creare un ritmo con i piedi o con le mani. Per l'armonia ci è voluto più tempo, l'uomo ha dovuto modulare la propria voce nel canto e costruire strumenti in grado di emettere note.

L'armonia è proprio la dimensione verticale delle note, la cui base è quello che i musicisti chiamano "accordo": non più una singola nota, bensì una sovrapposizione di voci più alte o più basse, strumenti diversi con timbri diversi. Quindi il ritmo come qualcosa di immediato, facilmente sintonizzabile dal cervello, una componente empatogena; l'armonia come costruzione per sovrapposizione di note, che mira al bello e straborda di emozioni.

La matematica è il motore dell'arte classica, la sezione aurea è stata usata da scultori, architetti e pittori per secoli. Anche la musica ne è stata permeata, dalle *Variazioni Goldberg* di Bach, alla *Sonata in Do Maggiore* di Mozart, alla *Sinfonia numero 5* di Beethoven, fino alla famosa *Filth of Fifth* dei Genesis. Difficile non pensare al numero aureo quando si guarda uno Stradivari o si disegna una chiave di violino. C'è chi legge nella struttura dei tredici tasti che compongono un'ottava del pianoforte (otto tasti bianchi e cinque neri, con questi ultimi raggruppati per due e per tre) addirittura un rimando alla serie di Fibonacci.

Ma è soltanto di rigide proporzioni e fredde sequenze numeriche che la musica si serve per essere apprezzata? Certamente no, tuttavia è utile ancora mantenere il nostro cervello sotto la veste matematica per seguire i prossimi brevi concetti di armonia musicale.

Il modo più semplice per parlare di armonia musicale è di riferirsi alla musica tonale, ovvero quella che crea una armonia intorno ad una nota (chiamata "tonica") sfruttando le altre note comprese nell'intervallo di ottava (quello che va ad esempio da un Do del pianoforte al Do successivo alla sua destra) della tonica scelta, seguendo una scala (successione di note imposta da precise regole) maggiore o minore.

Proviamo a fare ordine in questo insieme di nozioni: ogni scala possiede sette gradi (scritti in numeri romani) in cui la tonica occupa il I grado. Il V grado è chiamato "dominante", poiché esso è l'elemento armonico più forte della musica tonale: la successione dominante-tonica, con tutti gli accordi immaginabili costruiti sopra, determina un rafforzamento importante della tonalità espressa rispetto al solo accordo costruito sulla tonica. Il III grado ("mediante") viene usato per ottenere la varietà nell'armonia, in quanto cambia tra modo maggiore e minore, mentre il I e V grado (gradi forti) restano invariati nei due modi della scala. Da un lato il fondamento della tonalità (I e V), dall'altro il colore dato dal III. E insieme agli altri quattro gradi, combinandosi fra loro, generano l'armonia musicale.

Ora è il momento di creare delle melodie.

2.2 I PATTERN MUSICALI

La melodia è un gruppo di note avvertito come successione coerente, è la dimensione "orizzontale" della musica (mentre l'armonia è stata prima definita "verticale").

FIG. 1 F. Mendelssohn, *Quarta Sinfonia op. 90 "Italiana"*, su un piano cartesiano che correla la melodia (susseguirsi delle note) all'armonia (sovrapposizione delle diverse note).

Quando si canticchia o si fischietta fra sé e sé, ciò che viene riprodotto è la melodia: le diverse canzoni vengono riconosciute dal nostro cervello grazie ad essa e alla sua capacità di richiamare le informazioni archiviate nella memoria.

Se ogni successione coerente di note può essere definita melodia, perché tuttavia non ricordiamo l'intera sinfonia di Beethoven ma solo il suo motivo principale? Quello che viene ricordato è in genere il "tema", una melodia che ricorre più volte in una composizione. Questo principio è valido per la musica classica, ma anche per il jazz, dove ad esempio il tema può essere individuato tra una improvvisazione e l'altra. Anche nella musica pop o rock il ritornello viene ripetuto più volte nella canzone e sembra spesso entrare in testa e non uscirne più.

Tornando alle analogie col linguaggio viste nelle sezioni precedenti, una composizione musicale può essere vista come un discorso più o meno lungo fatto allo spettatore, che recepisce bene ciò che viene espresso con chiarezza e sottolineato più volte: è questa la funzione del tema. Quando si improvvisa mentre si esegue un brano musicale, non si fa altro che dialogare con il tema, variando e aggiungendo un tocco personale, per poi tornarvi inevitabilmente.

L'arte di creare temi "orecchiabili" non è di certo frutto dei giorni nostri. Nella raccolta di musica per cornamusa di William Dixon del 1733 cominciano a comparire dei motivi definiti qualche anno più tardi *piper's maggot* ovvero "baco del suonatore di cornamusa". La metafora entomologica era già evidente quindi, quando negli anni Ottanta del Novecento viene introdotto il termine di "earworms", che in italiano suona come "tarli nelle orecchie", per indicare i motivi ripetuti in testa in maniera quasi ossessiva dopo averli ascoltati.

Ma come mai il cervello può diventare così ossessionato dai motivi musicali? La causa risiede nella natura stessa della mente, che cerca continuamente di dare un senso e un ordine alle sue esperienze sensoriali. Grazie al fatto che l'informazione sonora viene temporaneamente conservata dal circolare dell'impulso elettrico nei centri della memoria a breve termine, la nota successiva può essere messa in relazione con la precedente e l'altra ancora e così via. Certamente viene a crearsi un ordine, un pattern costituito da diverse note, il modo preferito dal cervello di recepire uno stimolo sensoriale. L'aspetto più interessante è che una volta compreso qual è il tema del brano, il cervello continua a processare tutte le note alla ricerca di quel tema, opportunamente armonizzato.

Nella scorsa sezione è stata sottolineata l'importanza della successione dominante-tonica nel definire la forza della risoluzione di una tonalità: il cervello vuole sentire di nuovo l'accordo di tonica, non vuole essere lasciato "sospeso" su quello di dominante, specie se suonato come settima (accordo in cui è presente il settimo grado della scala costruita sulla dominante). Una volta individuato un pattern, il cervello inizia a seguire lo stimolo musicale cercando di prevedere le note che verranno sulla base di quelle appena esperite.

La gratificazione nel riconoscere nuovamente il pattern nel brano è il motivo per cui piacciono così tanto canzoni con temi chiari e ripetitivi: ovviamente l'altra faccia della medaglia è l'iniziale rifiuto nei confronti della novità, di brani che contengono molte variazioni o accordi particolarmente dissonanti e non legati da successioni armoniche. Questo, ad esempio, è il motivo delle iniziali critiche a composizioni come *Quartetto in Fa diesis minore* di Schoenberg o *Sagra della Primavera* di Stravinskij. Iniziali, poiché come per tutte le esperienze artistiche il cervello può essere educato all'esposizione a queste dissonanze e riuscire a godere comunque della ricerca di pattern, specie se nascosti dalla sovrapposizione di diverse melodie.

Al cervello non piace avere vita facile, quando rileva subito un pattern abbassa di molto il livello di attenzione al brano: per questo molti compositori di musica classica (e non solo) tendono a ritardare appositamente la risoluzione nell'accordo di tonica, per tenere i loro spettatori più attenti possibile e per suscitare in loro una tensione emotiva.

2.3 MUSICA ED EMOZIONI

Nel 1956 il musicologo Leonard Meyer scrive *Emozione e significato nella musica*. La sua idea è semplice ma rivoluzionaria: l'emozione musicale nasce dal dubbio e dalla confusione che la mente ha nel momento in cui cerca di ritrovare il pattern in una composizione musicale e la sua armonia nella risoluzione[5]. È per questo che Beethoven nel suo *Quartetto per archi in Do diesis minore* ritarda la risoluzione nell'accordo di tonica, lo fa suonare soltanto in maniera incompleta per la maggior parte del brano e lo conserva per il finale.

Cosa media nel cervello questa facoltà innata e a cui spesso non si fa neppure caso, ovvero provare emozioni? Lo stimolo musicale in viaggio all'interno del cranio (ormai il percorso si sta facendo sempre più lungo e intricato) è stato processato con freddezza nelle sue componenti più elementari e "sommato" per cercare di invidiarne i pattern. Con il termine "sommato" si intende sia l'aspetto verticale delle note, cioè l'armonia all'interno di un accordo, sia l'aspetto orizzontale, il ritmo del brano e il susseguirsi degli accordi ascoltati. Mentre sta avvenendo questa processazione dello stimolo, una quota non indifferente di impulsi nervosi giunge alle aree "primitive" del cervello, quelle che regolano la componente emozionale.

Come si misura in questi casi il grado di attività delle diverse aree cerebrali? I ricercatori espongono i soggetti a musica ad alto contenuto emotivo (verrà chiarito in seguito cosa si intende) e misurano, grazie a specifiche tecniche di imaging, quali aree stanno consumando più ossigeno. L'effetto è definito "autoregolazione del flusso cerebrale" (o accoppiamento flusso-metabolismo): nelle aree più attive durante un compito, ad esempio ascoltare musica, arriva più sangue poiché serve più ossigeno per lavorare al meglio. Per musica ad alto contenuto emotivo si intende una melodia armonizzata con accordi consonanti e accordi dissonanti disposti in modo da stridere un po' nell'esecuzione, ma facilmente isolabili.

Gli accordi consonanti seguono la teoria dell'armonia musicale trattata in precedenza, sono quelli che il cervello si aspetta di sentire, specie la risoluzione sulla tonica. Gli accordi dissonanti invece sono quelli che restano sospesi, come la settima di dominante che deve risolversi sulla tonica, il cervello lo esige.

Aprendo una piccola parentesi, uno degli accordi più dissonanti della teoria musicale è il "tritono" (intervallo di quarta aumentata o quinta diminuita). Durante il Medioevo, era chiamato *diabolus in musica* e il suo utilizzo era praticamente proibito ai compositori. Infatti, il tritono tende fortemente a risolversi, ma il nostro

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[5] L.B. Meyer, *Emotion and Meaning in Music*, Chicago, The University of Chicago Press, 1956.

cervello non riesce a capire se la risoluzione va verso il grado più in alto o più in basso: neanche i musicisti più esperti distinguono se la sequenza è ascendente o discendente e si genera il "paradosso del tritono".

Tornando ai centri delle emozioni musicali, i neuroscienziati hanno scoperto che l'ascolto di un accordo consonante attiva, tra le tante, un'area sottocorticale che si chiama "nucleo accumbens" e un'altra area che fa parte della corteccia prefrontale, detta "orbitofrontale"[6].

Traduzione: il cervello gode nell'ascoltare la consonanza, nel vedere rispettati i pattern intuiti (gode, esattamente; il nucleo accumbens è considerato il centro del "piacere" o della "ricompensa" cerebrale); la corteccia orbitofrontale è decisione, una componente arcaica della decisione, legata al meccanismo di piacere e ricompensa. "Fa' questa cosa perché proverai piacere, ascolta questa consonanza, è un qualcosa di positivo" potrebbe suggerire il cervello a questo gruppo di soggetti sperimentali. L'ascolto di un accordo dissonante, invece, stimola un'altra porzione del cervello arcaico (che gli anatomisti chiamano "sistema limbico" per la sua forma come a contornare le strutture al centro dell'encefalo) che si chiama "giro paraippocampale": esso è legato al processo di memorizzazione e proietta le sue fibre nervose all'"amigdala", una piccola struttura a forma di mandorla che in prima approssimazione si attiva quando si prova paura. L'accordo dissonante genera emozioni, ma spiacevoli, quelle che scendono nel tronco encefalico provocano la famosa reazione di "attacco o fuga".

Ovviamente, ascoltare un tritono non fa correre via nessuno dalla sala, ma seguire per minuti oppure ore una composizione basata sulla dissonanza (come la già citata *Sagra della Primavera* di Stravinskij) può davvero generare un aumento del battito e una accelerazione del respiro, specie se si è seduti nelle prime file di un grande teatro. L'amigdala proietta anche in un altro pezzo di corteccia prefrontale, chiamata "ventromediale", che influenza le decisioni sì, ma nel senso opposto rispetto alla orbitofrontale: "evita ciò che genera paura", direbbe.

Quindi, non va sottovalutato il potere della musica nel suscitare emozioni, le sue connessioni sono dirette e non necessitano di troppe elaborazioni corticali: parlano "alla pancia" del pubblico. Certo che una divisione così netta tra accordi buoni e cattivi, tra cervello che preme o solo sull'acceleratore o solo sul freno, deve essere vista come puramente esplicativa. La forza e la bellezza dell'emozione musicale risiedono proprio nell'alternanza degli stati d'animo che si provano continuamente durante le

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[6] C.J. Limb, *Structural and Functional Neural Correlates of Music Perception*, in *The Anatomical Record Part A*, 288(4), p. 20.

esecuzioni, sia per le orecchie di chi ascolta sia per le mani di chi suona. Su questi principi si possono costruire melodie “catchy” per il pubblico e ripresentarle quasi invariate per un intero disco. Una critica alla tendenza contemporanea di scrivere musica ad hoc per le radio è proprio l’appiattimento emotivo che crea nell’ascoltatore. Ovvio che stimolare i centri della ricompensa (estate dopo estate, singolo dopo singolo) con accordi consonanti e pattern di immediata lettura favorisce un discreto ritorno in termini di ascolti, quindi anche economici. Ma educare alla varietà, all’accordo ricercato, al ritmo che muta nel brano è fondamentale. Ne parleremo.

Ora è giusto spendere ancora qualche parola per chiudere il cerchio delle connessioni ricamate dalla musica nel cervello, prima di lasciare il sistema limbico. Sta per terminare il lungo viaggio delle note, partite da lontano sul palco, attraversando la sala e l’orecchio e il nervo acustico e il tronco encefalico e le varie cortecce e i centri delle emozioni: vi ricordate?

2.4 LA MEMORIA

Clive Wearing è un musicista e musicologo britannico che nel marzo 1985 a quasi 47 anni viene colpito da una encefalite erpetica (una grave infezione del cervello causata dal comune virus che in genere porta all’herpes sul labbro, ma in rarissimi casi può danneggiare anche estese aree cerebrali). Clive esita con un danno pressoché totale ai centri della memoria: non riesce a ritenere una informazione nuova per più di qualche secondo, oltre ad avere una devastante perdita dei suoi ricordi passati.

La moglie Deborah scrive nel suo libro *Oggi, per sempre* del 2005 alcune delle frasi pronunciate da Clive nei mesi successivi: «[...] era come se ogni risveglio fosse il primo [...] io non ho mai ascoltato niente, visto niente, toccato niente, annusato niente [...] è come essere morto»[7].

Passa i primi sette anni di malattia in unità psichiatrica per cronici, gli unici momenti in cui si sente vivo sono le visite di Deborah, di cui lui purtroppo dimentica non appena lei varca la porta. *Una storia d’amore oltre la memoria*, suonerebbe così il sottotitolo in italiano del suo libro.

Torna a casa dopo questo periodo in clinica e col passare degli anni la sua socialità migliora e sebbene la compromissione della memoria resti gravissima, con l’aiuto di Deborah e degli amici riesce a vivere una vita ancora piena di stimoli, anche andando a teatro e alle rappresentazioni musicali.

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[7] D. Wearing, *Forever Today, a true story of lost memory and never-ending love*, London, Corgi, 2005.

E la musica è un aspetto interessante della sua storia: già durante il soggiorno in clinica, Clive, pur non sapendo cosa fosse una partitura musicale, è in grado di leggere le note e di cantarle. Tornato a casa, la sua capacità di suonare il pianoforte si rivela intatta, così come l'abilità di improvvisare su un brano seguendo le regole dell'armonia musicale (che ovviamente non riesce ad esplicitare a causa dell'amnesia).

Un uomo con una finestra di memoria dell'ordine dei secondi come può leggere la musica e suonare perfettamente un pianoforte? Già nel 1957 con il caso del paziente amnesico più famoso della storia, H.M., appare evidente una separazione tra due tipi di memoria diversi: una esplicita (cosciente) e una procedurale (non cosciente). Clive ha perso la sua memoria esplicita, sia nella sua forma semantica (richiamare e immagazzinare termini o nozioni) che episodica (legata agli eventi della vita); tuttavia la memoria procedurale rimane intatta, dal prendersi cura del sé della quotidianità al suonare il pianoforte. Ovviamente anche ad un esecutore come lui non basta la memoria procedurale, occorre anche quella esplicita per ricordare quale brano sta preparando, senza essa non avrebbe neppure voglia di studiarlo. Egli deve essere guidato in questo, ma l'atto in sé appare naturalmente conservato.

Le teorie delle basi neurologiche della memoria negli ultimi cento anni sono state innumerevoli e ancora oggi la ricerca è impegnata ad indagare cosa accade a livello cerebrale quando si incamera un ricordo esplicito o implicito e quando lo si recupera. Dal caso H.M. si è compreso il ruolo centrale dell'ippocampo (una struttura del sistema limbico visto nella scorsa sezione) nella memoria semantica ed episodica e nel consolidamento della memoria a breve termine (operativa, che dura qualche minuto) a memoria a lungo termine (che dura anni o tutta la vita).

L'ippocampo è uno snodo fondamentale del sistema limbico: quando l'informazione vi giunge, circola nel lobo limbico più e più volte, come fosse un circuito che sfrutta la forma anatomica di "limbus". Le proiezioni sulla corteccia sono quelle che probabilmente fissano la memoria esplicita (le informazioni in corteccia sembrano essere ritenute dalle ampie connessioni tra le varie aree cerebrali, piuttosto che incamerate in singole porzioni di cervello). Il legame con le emozioni, sia positive che negative, è evidente: infatti le emozioni influenzano la formazione e il richiamo di ricordi. La corteccia inoltre deve essere in grado di recepire l'informazione che arriva dal circuito limbico e in questo il livello di attenzione è fondamentale.

La memoria procedurale sembra più legata alla componente motoria e quindi risiederebbe nelle aree del sistema motorio, come cervelletto e nuclei della base (strutture profonde distinte dalla corteccia): potrebbe essere una spiegazione del fatto che spesso nelle amnesie la capacità di richiamare ed imparare procedure inconsciamente è mantenuta; infatti, queste regioni sono al di fuori dell'esperienza conscia corticale. Tuttavia, anche in questo caso si tratta di una estrema semplificazione, poiché la corteccia è fondamentale anche nella memoria procedurale, soprattutto nell'apprendimento motorio, ma l'argomento è molto vasto e il concerto troppo breve.

I cinque musicisti sul palco stanno stimolando da qualche pagina le menti degli spettatori in sala, suscitando in loro emozioni diverse e richiamando alla mente (con delle cover di brani più "classici") qualche esperienza legata al primo ascolto di quella canzone, magari un falò in spiaggia, il cielo sopra una tenda, un viaggio rocambolesco e così via. Dunque, più di un qualcosa è accaduto nella mente del pubblico, dai freddi impulsi nervosi ne è nata la percezione della melodia e di tutta la sua componente emotiva. Molti spettatori hanno ascoltato spesso musica durante tutta la loro vita ed alcuni suonano persino un qualche strumento, come i musicisti sul palco. L'ascolto e la pratica musicale stimolano così tante aree cerebrali che ci si meraviglierebbe di scoprire che col passare del tempo non vi sia alcuna influenza sulla struttura e sulla funzione del cervello. E infatti non è così, anzi.

Sarebbe interessante discutere di questo durante le ultime canzoni.

A cosa faccia appello la musica in noi è difficile sapere; è certo però che tocca una zona così profonda che la follia stessa non riesce a penetrarvi.

Emil M. Cioran

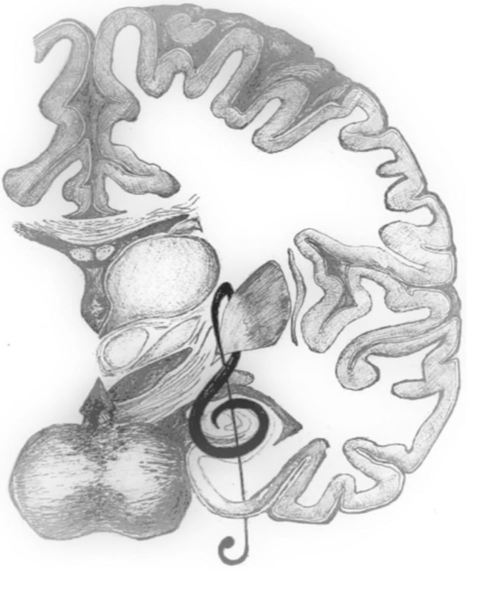

FIG. 2 Disegno a penna ispirato ad una sezione frontale dell'encefalo con una "chiave di violino" inscritta nell'ippocampo (per gentile concessione di Irene Mazzarella).

3. GLI EFFETTI DELLA MUSICA SULLA MENTE

3.1 IL CERVELLO DEI MUSICISTI

Oggi gli anatomisti avrebbero serie difficoltà a identificare il cervello di un individuo particolarmente versato nelle arti visive, oppure quello di uno scrittore o di un matematico; ma potrebbero riconoscere il cervello di un musicista di professione senza esitare un solo istante[8].

Oliver Sacks

Ha davvero ragione Sacks quando afferma un concetto così netto? Al di là delle oggettive difficoltà nel dimostrare questa affermazione, non ci sono dubbi sul fatto che il suonare uno strumento musicale per diversi anni modifichi alcune strutture cerebrali.

Il cervello è composto da cento miliardi di neuroni, ciascuno dei quali può potenzialmente avere migliaia di connessioni, sinapsi, diverse (tralasciamo la stima di quanti diversi circuiti possono formarsi al suo interno). Si pensa che le differenze tra musicisti e non-musicisti siano dovute proprio al rimodellamento di queste connessioni (anche se la scoperta di neuroni in grado di rigenerare potrebbe in futuro rivisitare queste teorie ed aprire nuovi interessanti scenari).

Entra in scena il concetto di "plasticità", piuttosto in voga negli ultimi anni: è l'insieme delle variazioni dell'organizzazione nervosa. Essa è la base per potersi adattare ai cambiamenti dell'ambiente circostante e per poter compensare eventuali danni al tessuto nervoso, come lesioni di vario tipo o l'invecchiamento. Dunque, i musicisti stimolano alcune aree cerebrali più dei non-musicisti ed esse rispondono tramite fenomeni di plasticità nervosa con un potenziamento della loro funzione. Occorre come sempre dare qualche definizione prima di cominciare.

La plasticità può essere strutturale o funzionale: il termine "strutturale" indica un cambiamento della morfologia del cervello, ad esempio aumento o riduzione delle connessioni; il termine "funzionale" invece si riferisce ad una riorganizzazione cerebrale, senza un cambiamento nella morfologia vero e proprio. Nei musicisti avvengono entrambi questi fenomeni e il tutto porta ad una complessità di interazioni che è piuttosto difficile da riassumere in poche righe.

Un altro aspetto da sottolineare è che più precoce e più lunga è l'esposizione alla pratica musicale maggiore è l'effetto di modellamento cerebrale: l'aumento di volume di una regione cerebrale è sinonimo di aumentata stimolazione ed è conseguenza

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[8] O. Sacks, *Musicofilia, racconti sulla musica e il cervello*, traduzione di Isabella Blum, Milano, Adelphi, 2009.

della plasticità strutturale. L'aumento di attività in una regione non precedentemente correlata alla stimolazione di una data regione è invece indice di plasticità funzionale.

Quindi i ricercatori hanno sfruttato delle tecniche di imaging cerebrale per confrontare musicisti e non-musicisti e quello che ne è venuto fuori è stato in parte in linea con le aspettative e in parte più interessante[9]. I pianisti hanno aree corticali legate alla motricità della mano sinistra più sviluppate rispetto ai non-musicisti e lo stesso vale anche per coloro che suonano strumenti a corda, come chitarristi e violinisti. Anche la corteccia sensitiva corrispondente è più estesa. Inoltre, il lobo temporale, legato – come è già stato descritto – alla percezione delle note e delle melodie, presenta diverse aree più rappresentate nei musicisti. Il Planum Temporale, lo stesso visto parlando di orecchio assoluto, è maggiormente lateralizzato nei musicisti: va ricordato quanto esso sia importante anche nell'ambito del linguaggio, così come le altre strutture del lobo temporale. Il cervelletto dei musicisti è implicato nell'apprendimento motorio e quindi segue le differenze viste per la corteccia motoria.

Molto interessante è il riscontro di differenze in aree di corteccia definite "associative", cioè dove si integrano le informazioni provenienti dalla vista, dall'udito, ma anche dal corpo stesso. Un fenomeno piuttosto diffuso tra i musicisti è quello della "sinestesia", ovvero una contaminazione tra i diversi sensi della percezione. Suonare o ascoltare una nota o un accordo può associarsi ad esempio all'esperienza di percezione di un colore in maniera così stretta che si può provare persino fastidio nel provare ad associarne un altro.

Infine, il rafforzamento di alcune connessioni promosso e sostenuto dalla musica può essere utilizzato ad esempio per recuperare alcune funzioni cerebrali perse o quanto meno rallentarne la perdita.

3.2 La musicoterapia

Anche se spesso non vi si fa troppo caso, l'ascolto della musica avviene per una gran quantità di tempo nell'arco della vita. Come sottofondo di un caffè in un bar, nei pomeriggi di studio, nei negozi di ogni genere la musica accompagna le giornate di centinaia di milioni di persone. Immaginare un mondo senza musica è quasi impossibile per chi non presenta nessun difetto delle vie descritte nelle sezioni precedenti.

Pensare che questo attributo del mondo possa migliorare la qualità di vita di alcune tipologie di pazienti è forse ancora più difficile da credere. Eppure, nella sezione pre-

[9] C. Gaser, G. Schlaug, *Brain Structures differ between Musicians and Non-Musicians, in The Journal of Neuroscience*, 23(27), 2003.

cedente si è segnalato come l'esposizione alla musica possa modificare alcune regioni cerebrali: certo ascoltare una playlist mentre si corre nel parco non avrà lo stesso effetto di studiare violino per anni, tuttavia, tralasciando per un momento il risultato finale, si è cercato di capire se e come la musica possa avere effetti sulla attività cerebrale.

Intanto: i musicisti professionisti sono effettivamente più protetti della popolazione generale dal fisiologico declino cognitivo legato all'invecchiamento. Il deterioramento cognitivo è una riduzione dell'efficienza legata all'età nei domini della memoria, dell'attenzione, dell'apprendimento e del linguaggio. C'è una estrema variabilità sia nella velocità che nella gravità del quadro nella popolazione.

Il motivo è proposto dagli scienziati con la teoria della "riserva", distinta in riserva cerebrale e cognitiva. Per riserva cerebrale si intende l'insieme delle capacità cognitive all'inizio del deterioramento, legata alla quantità di neuroni e connessioni presenti. Sembra un concetto molto smile a quello di plasticità strutturale e in effetti chi nella vita ha stimolato maggiormente alcune aree cerebrali potrebbe vederne ridurre il volume più lentamente. Invece, per riserva cognitiva si intende la capacità di adattamento dei circuiti neurali alla perdita delle connessioni età-correlata. Ancora una possibile analogia con la plasticità funzionale vista in precedenza.

La teoria chiaramente non mantiene separate queste due "riserve", ma nello stesso momento e nel singolo individuo possono intervenire in diverso grado per spiegare perché alcuni sono meno soggetti al declino cognitivo di altri. Le attività culturali, come lo studio o la pratica e ascolto della musica, lavorano su entrambe le componenti della riserva.

Studiando ad esempio i musicisti delle orchestre[10], con età dal giovane adulto all'anziano, e confrontandoli con soggetti non-musicisti delle stesse età, si sono osservati diversi elementi interessanti: i non-musicisti mostrano, con l'avanzare dell'età dei soggetti, una riduzione del volume totale degli emisferi e in particolare di alcune aree come la corteccia prefrontale, cosa che non avviene nel gruppo dei musicisti. Al momento non sono chiari i meccanismi biologici più fini alla base di questi risultati, ma il fatto che alcuni studi riportano delle performance legate alla comprensione linguistica e alle abilità visuo-spaziali superiori dei musicisti rispetto ai non-musicisti fa ben sperare la ricerca in questo ambito: il rallentamento del declino funzionale emerge, il miglioramento della qualità di vita anche, va solo capito come esso avvenga.

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[10] V. Sluming *et al.*, *Voxel-Based Morphometry Reveals Increased Gray Matter Density in Broca's Area in male Symphony Orchestra Musicians*, in *NeuroImage*, 17(3), 2002.

È importante puntualizzare che ogni speculazione sull'uso terapeutico della musica è limitata all'aspetto preventivo o all'accompagnamento delle cure farmacologiche, specie nei quadri più gravi. Il suo bassissimo costo, la possibilità di formare terapeuti qualificati e il suo potenziale contatto emotivo con il paziente rende la "musicoterapia" una realtà sempre più affermata, in particolare nel mondo anglosassone.

Il tredicesimo Congresso Mondiale della WFMT (*World Federation of Music Therapy*) nel 2011 la definisce come «l'uso professionale della musica e dei suoi elementi come intervento in ambienti medici, educativi e sociali con individui, gruppi, famiglie o comunità che cercano di ottimizzare la loro qualità di vita e migliorare la salute e il benessere fisico, sociale, comunicativo, emotivo, intellettuale e spirituale»[11]. Accompagnare una terapia volta a contrastare la causa organica di una malattia con tipologie di intervento come la musicoterapia o analoghe ha il vantaggio di riportare il paziente al centro del programma terapeutico (in questi casi è il paziente che guida attivamente il terapeuta).

Al di là delle diverse tecniche che si possono utilizzare in questo tipo di terapia, l'idea di centralità della figura del paziente deve essere uno spunto di riflessione per tutte le branche della medicina contemporanea, per evitare l'uso esclusivo di metodi "alternativi" di cura da parte di pazienti che non si sentono compresi dall'approccio farmacologico o chirurgico, che tuttavia è fondamentale nella stragrande maggioranza dei disturbi medici.

A volte basta davvero poco per ottenere enormi risultati. Per quanto riguarda l'approccio basato sulla musica, esso può aiutare l'apertura sociale ed emotiva di soggetti affetti da autismo, può richiamare alla mente concetti o ricordi in quelli affetti da demenza, può (anche se con molta meno efficacia) ridurre le disfunzioni conseguenti ad un disturbo del movimento grazie alla immediatezza della componente ritmica della musica.

È un mondo ancora da esplorare, ma che propone sempre più spunti interessati. Agli spettatori appare sempre più chiaro quanto la musica faccia bene a tutte le età, dai più grandi ai più piccoli.

3.3 EDUCARE ALLA MUSICA

Quando si è impegnati nell'ascolto o nella pratica musicale, molte aree cerebrali cooperano tra loro: ormai questo è chiaro. L'importanza di questa cooperazione ha

[11] 13th World Congress of Music Therapy (Seoul, Korea 2011).

suscitato l'interesse di chi si occupa di pedagogia e ci si è chiesti se la musica potesse avere un ruolo nell'educazione dei bambini.

Fermo restando che tutte le modificazioni che la musica induce a livello cerebrale si attuano per tutta la durata della vita, sebbene con velocità e caratteristiche diverse, non vi è dubbio che tutto questo accade nel bambino in maniera più marcata.

Il motivo è biologico: nei primi anni di vita i fenomeni di plasticità strutturale e funzionale sono favoriti dall'architettura delle connessioni cerebrali, che si perdono e si riformano a velocità molto superiori rispetto alla vita adulta. Questo implica che l'apprendimento è più rapido ed efficace da bambini che da adulti.

Osservando per un momento l'essere umano non nella sua dedizione alle arti, alla filosofia, alla scienza, ma nella sua dimensione all'interno del regno animale, si capisce come l'evoluzione premi questa esplosione della capacità di apprendimento nei primi anni di vita. Senza dubbio i cuccioli di qualsiasi specie animale sono i più esposti della famiglia o del branco all'attacco dei predatori e la loro protezione mette a rischio anche tutti gli altri. Per fortuna, la nostra specie riesce in genere a garantire ai suoi "cuccioli" la tranquillità necessaria per poter raggiungere il pieno sviluppo dei suoi domini cognitivi e motori.

La complessità del nostro cervello fa sì che l'essere umano abbia un periodo critico molto lungo. Il "periodo critico" è una fase di maturazione di un organismo nella quale il sistema nervoso è particolarmente sensibile a determinati stimoli ambientali. La vista, ad esempio, nel bambino viene costruita connessione dopo connessione nelle prime settimane di vita, mentre l'occhio è già pronto praticamente dalla nascita a mostrare immagini (all'inizio molto sfocate e con colori poco distinti). Se uno o entrambi gli occhi non funzionano correttamente occorre intervenire il prima possibile, perché dopo un periodo relativamente breve la vista non sarà più in grado di svilupparsi. Per quanto riguarda l'udito i tempi si allungano a pochi anni, ma è comunque fondamentale un riconoscimento rapido di eventuali problemi di udito, perché risolverli potrebbe voler dire non avere problemi ad apprendere correttamente il linguaggio parlato.

Sul linguaggio e lo sviluppo del bambino si potrebbe discutere a lungo, ma tornando alla musica si è visto come in effetti porti a delle modificazioni a livello cerebrale anche nel bambino. Alcuni ricercatori[12] hanno sottoposto a training musicale per 15 mesi dei bambini di età intorno ai 6 anni e li hanno confrontati con bambini non sottoposti a questo allenamento nella musica con età analoghe. Ovviamente lo

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[12] K.L. Hyde, G. Schlaug, *The Effects of Musical Training on Structural Brain Development*, in *Annals of the N.Y. Academy of Sciences*, 1169: 182-186, 2009.

scopo di questi esperimenti è diversificare un poco i programmi didattici aggiungendo anche delle ore di musica per valutare se accade qualcosa nel cervello di questo gruppo di bambini: siamo a scuola, non in laboratorio. Quello che, con metodi non pericolosi e non invasivi, si è visto dopo 15 mesi è che le cortecce uditive e quella motoria (entrambe maggiormente nell'emisfero destro) sono più sviluppate nei bambini sottoposti a training. Inoltre, sono più sviluppate le connessioni tra i due emisferi che compongono quella regione cerebrale denominata "corpo calloso". Oltre all'aspettato miglioramento nei test ritmici e melodici e il maggiore sviluppo delle aree deputate all'ascolto delle note e alla motilità delle mani, è interessante notare l'aumento della connettività interemisferica che può facilitare l'apprendimento o migliorare le performance cognitive su diversi fronti.

Insomma, la musica può solo far bene ai cittadini del domani: essa favorisce la creatività, la socializzazione, la cooperazione, l'interazione fra culture diverse. L'educazione musicale deve seguire i principi di individualizzazione e personalizzazione: vi è infatti la necessità di portare ad un livello fondamentale di competenze musicali tutti gli alunni, in tempi diversi e con metodi didattici diversi (individualizzazione), ma al tempo stesso occorre promuovere e sostenere il talento musicale del singolo alunno, stimolandolo anche con percorsi didattici differenti (personalizzazione).

I talenti nella musica si vedono già da piccoli, ma senza una organizzazione scolastica che espone i bambini sia all'ascolto che alla pratica musicale spesso questi talenti non vengono riconosciuti. Inoltre, gli aspetti positivi della musica sulle funzioni cognitive e di relazione interpersonale sono utili in tutti i bambini, ma forse ancor di più nei bambini con disturbi specifici dell'apprendimento, dove la musica può rompere le barriere che purtroppo possono venire erette dal bambino stesso o dal contesto sociale e scolastico che lo circonda. Interazione, creatività, emotività, la musica insegna tutto questo.

E quando l'ultima variazione sull'accordo di Do settima sta scomparendo dagli amplificatori, con un gioco di sguardi simile a quello che ha dato il via all'esibizione tutti insieme mettono le dita sull'accordo di Fa maggiore e chiudono il concerto.

Il viaggio delle note all'interno del nostro orecchio, attraverso binari nervosi, è giunto a destinazione nella nostra mente. La melodia ha suscitato emozioni, rievocato ricordi, sviluppato tutto il suo potenziale benefico tra i più grandi e i più piccoli.

La musica è stata scomposta, poi ricomposta, il cervello scomposto, poi ricomposto.

Forse il mistero dietro al ruolo della musica nella nostra evoluzione per il momento resterà un mistero, ma oggi è chiaro quanto importante sia la musica anche nella prospettiva di ricerca scientifica. E l'essere umano è in grado di plasmarla, come ha plasmato il mondo da quando è comparso sulla Terra: egli è in grado di produrre quanto di più pericoloso, bello, sovversivo ed emozionante possa esistere. Degli accordi, una melodia, una poesia, una canzone.

La musica ci insegna la cosa più importante che esista: ascoltare. [...] la musica è come la vita, si può fare in un solo modo: insieme.

Ezio Bosso

BUILDING LIFE FROM THE BOTTOM

LEONARDO MORINI

Half a century after the discovery of DNA double helix and the Miller-Urey experiment on the chemical origin of life, the idea that biological systems could be handled with an engineering approach was common. Scientists from different backgrounds merged together to take on the challenge of modifying living organisms in a machine-like fashion. A smaller niche is now trying to push cellular lifeform to the limits: some by removing the unessential, others by assembling lifeless pieces from scratch. The latter way, among the highest examples of modern man's *hybris*, is also one of the greatest challenges of our century. But what has the path of artificial cells been up to now? Who is leading the field today? What technologies are needed for such a sci-fi intent and what are the consequences of all this? In the present work we recapitulate the milestones and the technological advances of artificial cell research. We expand the description with current efforts worldwide and illustrate different predictions about the synthetic lifeforms to come.

Mezzo secolo dopo la scoperta della struttura a doppia elica del DNA e dopo l'esperimento di Miller-Urey sull'abiogenesi, l'idea che i sistemi biologici potessero essere trattati con un approccio ingegneristico era ormai condivisa. Scienziati da disparate discipline si sono riuniti nel tentativo di modificare gli organismi viventi come se fossero macchine. Al giorno d'oggi, un piccolo gruppo sta spingendo il concetto di cellula al limite: alcuni togliendo funzioni non necessarie, altri assemblando da zero frammenti inanimati. Questa seconda strada, tra i più alti esempi di *hybris* dell'uomo moderno, è anche una delle sfide più grandi del nostro secolo. Ma qual è stato il percorso delle cellule artificiali fino ad oggi? Chi sta guidando questo campo di ricerca? Quali sono le tecnologie necessarie per un intento così fantascientifico e quali saranno le conseguenze di tutto ciò? Nel presente lavoro ripercorriamo le tappe fondamentali e i progressi tecnologici della ricerca sulle cellule artificiali. Estendiamo poi la descrizione con i vari progetti presenti oggi nel panorama mondiale e illustriamo diverse ipotesi sulle future forme di vita sintetiche.

PREFAZIONE

Tra le domande fondamentali che appartengono alla riflessione interiore di ogni essere umano c'è sicuramente quella che si chiede da dove veniamo, da dove e come abbia avuto inizio la vita. Per molti secoli la risposta è stata prevalentemente di natura filosofica; solo dal XVII secolo in poi sono cominciate le prime sperimentazioni per tentare di fornire una risposta scientifica. Dimostrato che la vita non ha origine spontanea ma deriva da altra vita, era inevitabile applicare un principio ex-causa attraverso il quale cercare di risalire all'evento originale che ha iniziato il processo di formazione della vita stessa. Nella prima metà del XX secolo ci si è dedicati a dimostrare la teoria di Darwin attraverso gli studi naturalistici, paleontologici e genetici per definire e direi confermare che la vita è fondamentalmente un processo instancabile di trasferimento da una generazione alla successiva di quell'"alito vitale" che sopravvive anche senza che si mantenga la stessa struttura biologica, la quale, invece cambia in funzione dell'ambiente e della selezione naturale. Ho usato volutamente l'espressione "alito vitale" ad indicare quel momento della scienza che ha trattato di vita senza averne colto fino in fondo la profonda natura fisica. L'identificazione nel 1953 della struttura del DNA come la molecola informazionale che contiene tutte le regole per costruire un organismo, e una visione riduzionistica della biologia dettata dalla fiorente biochimica degli anni Venti e Trenta, hanno permesso nella seconda metà del XX secolo di cercare non solo di capire come la vita si organizzi a livello molecolare ma addirittura di pianificare esperimenti che ne dimostrassero in qualche modo il meccanismo d'inizio. La prima teoria di una possibile origine chimica della vita appartiene al russo Alexander Oparin verso la fine del XIX secolo. Secondo Oparin, la vita sarebbe comparsa sul nostro pianeta a partire da una lunga catena di eventi che prende il nome di evoluzione chimica. L'ambiente primitivo sede dell'evoluzione chimica avrebbe avuto alcune proprietà fondamentali: l'ossigeno libero era quasi del tutto assente nell'atmosfera che, però, abbondava di idrogeno, mentre sia l'atmosfera che le acque presentavano importanti percentuali di azoto e carbonio. Sulla scorta di questa ipotesi, Miller e Urey nel 1953 tentarono di dimostrare che quel bordo primordiale poteva essere l'ambiente ideale per la formazione di molecole organiche quali alcuni amminoacidi. Pochi anni dopo Joan Orò dimostro che l'aggiunta di ammoniaca e acido cianidrico al brodo primordiale poteva produrre una base azotata come l'adenina. Sembrava fatta. Immaginando questi processi nell'alveo dell'evoluzione, era ragionevole ritenere che la semplicità di un amminoacido o di una base potesse su tempi lunghi trasformarsi in qualcosa di strutturalmente più complesso come per esempio un polimero. Questi studi tuttavia non ebbero gli sviluppi sperati e i loro risultati rimasero congelati nella "hall of fame" della biochimica. Dovettero passare altri trent'anni prima che Tom Cech, un giovane chimico dell'Università del Colorado scoprisse alcune piccole molecole di RNA lunghe qualche decina di nucleotidi e dotate di proprietà enzimatiche. In definitiva quei piccoli RNA potevano ben essere i brevi polimeri di acido nucleico che la teoria dell'evoluzione chimica aveva preconizzato molti anni prima. Questi piccoli RNA, identificati in alcun i protozoi, quali Tetrahymena, sono chiamati "ribozimi" ovvero molecole fatte di solo RNA in grado di maturare attraverso un meccanismo auto-catalitico di taglio e cuci. Questa scoperta, che fu premiata con il premio Nobel, dimostrava per la prima volta che un semplice acido nucleico formato da sole quattro basi era in grado di svolgere attività enzimatiche ritenute fino a quel momento di esclusiva proprietà delle proteine. La scoperta di Tom Cech apre il via al mondo di SELEX (Systematic Evolution of ligands by exponential enrichment) una tecnica di evoluzione vitro che porterà nel giro di un decennio a identificare centinaia di RNA sintetici in grado di mimare e svolgere essenzialmente tutte le reazioni enzimatiche fisiologicamente svolte in natura dalle proteine. Questi RNA aprono così l'ipotesi ad un "RNA world" ovvero un mondo al confine tra vita e non-vita che precede di uno, forse due, miliardi di anni il mondo del DNA e delle proteine che oggi conosciamo. Questo mondo a RNA è pensato come una cellula aperta nel cui plasma, tuttavia coesistono numerose reazioni enzimatiche svolte da piccoli RNA, molte della quale ancora presenti nella cellula che oggi conosciamo. L'idea di una vita risultante da sole molecole e quindi potenzialmente "decostruibile" e per lo stesso motivo "ricostruibile" ha dato origine ai giorni nostri a sfide ancora più grandi quali per esempio quella di tentare di produrre una cellula in vitro completamente artificiale. Alcuni lavori recenti hanno mosso i primi passi verso questo obiettivo dimostrando per esempio che è possibile sostituire il genoma naturale di una cellula procariotica o eucariotica con un genoma interamente generato per sintesi chimica.

Per saperne di più, il capitolo scritto da Leonardo Morini offre una raffinata e completa narrazione circa gli ultimi progressi di questa nuova scienza. Morini mette in risalto non solo gli straordinari risultati raggiunti fino ad oggi ma soprattutto evidenzia le problematiche inattese e le difficoltà che sono emerse durante le fasi di sperimentazione.

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I. ENGINEERING LIFE

I.I THE RISE OF SYNTHETIC BIOLOGY

In the last four decades of the twentieth century, the idea of a rational design of biological systems laid the foundations for the engineering field later known as synthetic biology. The period of the "awareness" of synthetic biology starts with the discoveries from Monod and Jacob. Their work on the *lac* operon (a structure of close genes regulated together for the same process) in *Escherichia coli* shed light for the first time on genetically-encoded regulatory features. With the arrival of the omics in the ninety's, that allowed analysis of large pools of molecules, the field of systems biology emerged and consolidated the connection between biology and computer science to unveil cellular networks.

The phase between 2000 and 2003 saw the implementation, study and tuning of several genetic regulatory circuits *in vivo*, mostly in *E. coli*. The most famous examples are oscillatory systems, such as the toggle switch and the *repressilator*, or the synthetic *quorum sensing* for engineered microbial communication. The boom of studies in the new discipline proved the need for a coordinated effort to standardize all the elements available for the community of synthetic biologists.

While gene circuitry advanced with logic gates, multicellular patterning and post-transcriptional regulation (such as riboregulators), in 2004 the MIT organized the first international conference. Synthetic Biology 1.0 showed the first attempt to create a collection of modular parts and protocols. The Registry of Standard Biological Parts, based on the BioBrick format, featured modular parts that could be assembled in any order thanks to arrays of restriction-enzyme sites. On the bioinformatic side, instead, Synthetic Biology Open Language set the standards for circuit design. Synthetic biology was being acknowledged at global scale with worldwide conferences and the founding of the iGEM, the renowned international student competition. After the discovery of CRISPR/Cas as a programmable system for genome targeting, regulative functions were quickly implemented by linking activator domains from transcription factors to the precise sequence-specific system. In the meantime, the J. Craig Venter Institute was working on the bacterium *Mycoplasma mycoides,* accomplishing the first interspecies genome transplantation in 2007 and, three years later, the creation and transplantation of the first functional synthetic genome into strain JCVI-syn1.0 (also known as *Synthia*). The second decade of 2000's saw advances in all the newborn fields [1]. Cello, a CAD software, allowed researchers to write a full plasmid sequence by only defining the logic gates of the desired circuit. In 2016, the J. Craig Venter Institute published the new release JCVI-syn3.0, with a minimized synthetic genome, a milestone for top-down synthetic biology. The synthetic genome mission expanded to *S. cerevisiae* with the Sc2.0 consortium and to *E. coli*, whose genome has been recoded to enable new codon allocations for non-standard amino acids.

These are only few of the landmarks of the growing community of synthetic biologists. Nevertheless, what might seem a one-way race to an artificial biology is only one side of the coin. Just as a tunnel being dug from both sides of a mountain, a parallel discipline has emerged in these same years, trying to master the rational design of biological systems from the opposite direction.

I.2 BOTTOM-UP AND TOP-DOWN APPROACHES

Two approaches prevail the field of synthetic biology. The top-down approach aims at thinning out the complexity of existing organisms by finding and removing non-essential features to reach what is known as the minimal genome. The bottom-up approach, instead, aims at the emergence of complexity by assembling inanimate biological elements together to create an artificial lifeform. The two approaches are not conceptually isolated, but rather they complement each other to discover what is necessary for maintaining biological processes *in vivo* and what is sufficient for recreating them *in vitro*, respectively, outlining the fundamentals of life in between. Interestingly, top-down and bottom-up studies seem to be academically separated: the first is usually a subject of life science laboratories, while the second belongs to physical science laboratories [2]. As a proof, the two main reviews on the history of synthetic biology cited in this work only accounted for the advances in top-down synthetic biology, thus disregarding the milestones in the bottom-up race for engineered cells [1, 3]. Only in few cases the two schools of thought were combined to give birth to *cellular bionics* interfacing living and synthetic particles [2].

I.3 ARTIFICIAL CELLS

Nowadays, synthetic biology has a myriad of facets: metabolic engineering, phage-based therapies, engineered probiotics and so on. Beyond these, one of the highest goals of synthetic biology is creating a synthetic lifeform. And in a world pervaded by the cellular paradigm this ambition is actualized in the artificial cell. As one might have noticed, "synthetic" and "artificial cell" have ambiguous meanings.

According to a few articles, “synthetic cell” refers to a particle that mimics a cell in shape or in any of its functions, but that is not necessarily *alive*. On the contrary, “artificial cell” is used to indicate a synthetic cell displaying the properties of life. For simplicity, this review will use the two terms interchangeably because there is no consistency throughout the cited articles and because we will only discuss about synthetic cells as entities to create life from scratch.

The first artificial cells should be as simple as possible: they should feature the minimum requirements to mimic life. Here the first issue arises: there is no absolute definition of life. We can define features of living organisms, but we cannot define life itself. This philosophical challenge is persistent in biology, for example in the endless debate about the status of viruses. Moreover, the features of life change depending on the magnifying glass we use to observe it. When looking closer at the cells, three qualities can be outlined, falling under the concept of autonomy:

- Informational autonomy: a system to maintain and propagate the sequence-based information (for example, DNA replication).
- Energetic autonomy: a basic metabolism to couple exergonic and endergonic reactions (i.e. spontaneous with non-spontaneous).
- Spatial autonomy: a boundary to separate the inner chemical space from the environment.

The first two features form the autocatalytic core of the system. The third, although not fully essential in principle (there might be boundary-less autocatalytic systems), allows for long-lasting thermodynamic spontaneity by maintaining chemical gradients in a far-from-equilibrium state. These concepts were first formulated in the theory of the *chemoton* (the chemical automaton) by Tibor Gánti in *The Principles of Life*, which set the basis to define the properties of protocells during the emergence of cellular life on Earth. However, this definition is biased as it is Earth-based. Another operative definition of life, more abstract and open for new solutions, describes it as a self-sustaining chemical system capable of Darwinian evolution [4]. In general, then, the autonomy of life was defined as the property of a “far-from equilibrium open system capable of an organizational identity through thermodynamic coupling of internal processes [5].

Still, the concept of autonomy of artificial cells is debated, like in the top-down research, where the minimal set of genes depends on what is provided by the human-controlled environment. A minimalist engineering can lead to a tiny set of encoded functions at the expenses of the performance of the cells, and it would require an increase in the complexity of the environment to compensate the biological deficit. For instance, the smallest genomes found in nature, *Nasuia deltocephalinicola* for the number of base pairs (112 Kbp) and *Tremblaya princeps* for the number of genes (120), are obligated endosymbionts, meaning that complex functions for their thriving are provided by the environment (in the stunning case of *T. princeps*, a further endosymbiont is present inside the cells of the first). In this sense, shifting the complexity from the cell to the environment would move the research away from the scope of studying the emergence of primordial life, which more likely resembled a ribonucleic acid-based replicator or a protocell. For this reason, prebiotic chemistry is an important field in bottom-up synthetic biology, studying molecules that carry out multiple functions in simpler environments.

2. MOTIVATIONS

Artificial cell research is driven by three purposes. First, following Feynman's paradigm of *creating for understanding*, a controlled assembly of an artificial cell would give deep insight into the fundamental processes of natural cells. The second relates to the emergence of life, as creating an artificial cell could shed light on the mechanisms that regulated prebiotic chemistry and the first protocells on Earth. The last one, instead, is about the applications in most biotechnological fields, from industry to biomedicine, due to the better efficiency of such controlled biological systems [2].

3. TECHNOLOGICAL BACKGROUND

The historical setting of artificial cells research is consequence of both theoretical and technological progress. As the paradigms of synthetic biology have already been introduced, we will focus here on the technological background the bottom-up school relies on.

3.1 CELL-FREE PROTEIN SYNTHESIS

Cell-free protein synthesis (CFPS) systems are fundamental for *in vitro* expression of synthetic genes. They consist of transcription and translation machineries, with the ability to carry out both processes in a one-step reaction, thus mimicking the cytosolic environment of a prokaryotic cell. The most used systems are TXTL and PURE [6].

TXTL system (which stands for Transcription and Translation) is based on *E. coli* lysate, added with amino acids and energy regeneration systems. Since it relies on the multi-subunit bacterial RNA polymerase with σ-factors, this system can carry out the expression of a wide range of genetic elements. On the other hand, the exact composition is not well defined and its performance is less reliable for characterizing standard parts for synthetic biology. Moreover, its top-down origin makes TXTL less eligible for fundamental research.

The PURE system (Protein synthesis Using Recombinant Elements), instead, is obtained with a bottom-up approach. All necessary macromolecules are purified from *E. coli* and added to the mix, that has then a definite composition [7, 8]. The transcription relies on the RNA Polymerase from bacteriophage T7, which consists of a single protein and has a rich library of characterized promoters for synthetic biology.

iSAT, (integrated rRNA Synthesis, ribosome Assembly, and Translation), is a further level in the CFPS. The transcription machinery expresses the ribosomal RNAs *in vitro* that, provided with ribosomal proteins, can carry out a functional translation. To this end, the PURE system is able to express almost all ribosomal proteins, being close to a self-replicating ribosomal assembly reaction [9].

3.2 COMPARTMENTALIZING SCAFFOLDS

Spatial autonomy is crucial for the modern life on Earth: a boundary to maintain two different chemical environments. In order for it to suit a cellular life-form, the ideal boundary should be biocompatible, semi-permeable, metabolically-regulated and capable of growth-division cycles. Potential scaffolds can be divided in 3 categories: membranous structures, emulsions and membrane-less coacervate [10].

Membranous scaffolds are composed by amphiphilic molecules (showing both a hydrophilic and a hydrophobic region) that can self-assemble above a specific critical concentration. Phospholipids can assemble in bilayers to form liposomes: these are the most studied scaffolds as their architecture is shared between the vast majority of biological membranes. Liposomes are permeable to small neutral molecules, but they rely on the presence of transmembrane channels for the exchange of large or charged solutes. Many bulk production methods are available (such as hydration, electroformation, water-in-oil emulsion transfer), but now they are being overcome by more sophisticated and precise microfluidic techniques. Unilamellar liposomes are classified according to their size: SUVs (small unilamellar vesicles) have a size range of 20-100 nm with an elevated membrane curvature, LUVs (large) range from 100 to 1000 nm and finally GUVs (giant) have a size above 1 μm. A second promising class of molecules is fatty acids (FA), that are studied as very plausible molecules in a prebiotic world. FA vesicles are permeable to a wider range of solutes and are less stable to temperature and pH changes compared to liposomes. However, since fatty acids precipitate very easily with divalent cations such as Mg^{2+}, they are incompatible with modern transcription and translation machineries. Other types of membranes include polymersomes, made of synthetic copolymers tunable in thickness, stability and permeability, as well as hybrid membranes obtained by mixing different amphiphiles.

Emulsion scaffolds are aqueous droplet suspended in an organic phase that can be efficiently produced with microfluidic techniques. Droplet interface bilayers can be obtained through contact between droplets, allowing for microcompartments and tissue-like networks. The water/oil interface can be further used for the self-assembly of particles forming a Pickering emulsion. These structures can be either made of inorganic colloids (forming colloiodosomes), proteins (proteinosomes) or polyelectrolytes (microcapsules). Pickering emulsion is a very versatile technique because it allows for a highly controlled multi-step scaffold preparation: once coated, the emulsion can be transferred into an aqueous phase, more suitable for solute exchange with the synthetic cell.

Coacervates, very common in nature, are formed by a liquid-liquid phase separation process that doesn't require a membrane. They usually involve electrostatic interactions between charged polyelectrolytes (such as RNA, proteins or polysaccharides). Coacervates have been proposed as basis for the primordial life for almost a century, thanks to their ability to create crowded local environments, mimicking the conditions of a cell. Although they don't guarantee selective permeability, coacervates open up the field of membraneless synthetic cells. Moreover, they can work as scaffolds for membrane formations.

3.3 MICROFLUIDICS

Droplets are the simplest compartment for mimicking cytosolic processes. Available protocols for bulk production are widely used, although the development of microfluidics is paving the way for highly controlled synthetic cells production and manipulation. Materials such as PDMS (polydimethylsiloxane) allow the creation of microfluidic chips that are biocompatible, cheap and adequate for manipulation and measurement of life-like particles. On these chips, droplets are generated in a flow junction, where an aqueous "cytosolic" phase is cut and encapsulated into an oil phase. The geometry of the chip allows for a strict control of shape and size. Vesicles can undergo pico-injections of defined compounds or they can be immobilized on the chip for further analysis [11]. Lately, droplets can be transferred to a second aqueous phase, forming controlled liposomes that can be produced at kilohertz rates. In addition, methods like the octanol-assisted assembly and the glass capillary-based enable the formation of complex structures such as vesosomes, i.e. liposome-in-liposome.

3.4 MEMBRANE FUNCTIONALIZATION

While cytosolic proteins are relatively simple to add to the internal aqueous phase, issues arise when proteins need to be integrated in the membrane. Membrane proteins cannot be added beforehand to the oil-phase and their activity relies on the proper folding and insertion of several transmembrane domains, as well as on their asymmetric orientation. Early methods for reconstitution of membrane proteins involved the spontaneous fusion of vesicles with plasma membranes or the detergent-mediated reconstitution. The latter allows to regulate the orientation of asymmetrically charged proteins by using charged phospholipids in the vesicle. Alternatively, the droplet transfer method allows to add micellar proteins either to the inner or to the outer aqueous solution before the liposome formation to control the orientation. Nowadays, simple membrane proteins can be assembled from the inside of the vesicle by expressing synthetic genes via CFPS. Moreover, the efficiency of this process has been improved by adding translocation systems inside the vesicles [12].

4. EARLY YEARS

The history of artificial cells finds its roots in the twentieth century's theories on the origin of life as they both share a synthetic paradigm. One of the milestone experiments comes from the Russian biochemist Alexander Oparin in 1965, who demonstrated that coacervates made of gum arabic and gelatin are able to entrap enzymatic activities and show reactions for starch metabolism. Decades later, the beginning of the new millennium saw the foundational works of the bottom-up approach on gene expression in lipid vesicles, with methods that are still in use today [13]. In 1999 the Italian group of Luisi synthesized polyphenylalanine peptides in vesicles using purified ribosomes and a poly(U) RNA template. The complete synthesis of a functional protein was achieved two years later by the Japanese group of Yomo. They used the T7 RNA polymerase and *E. coli* extracts to drive the expression of GFP. Along with the first Synthetic Biology conference, year 2004 is a landmark for bottom-up synthetic biology thanks to two revolutionary works. Yomo and colleagues integrated the first genetic cascade inside a liposome: the T7 RNA polymerase gene was expressed under the control of a SP6 promoter and regulated itself the expression of the green fluorescent protein (GFP). Noireaux and Libchaber, instead, encapsulated a CFPS system from *E. coli* into GUVs carrying out the expression of GFP. They managed to improve gene expression by expressing α-hemolysin, that self-assembled in the membrane to form a pore that favored intake of substrates from the environment [14].

5. AROUND THE WORLD

Although independent laboratories worldwide converged towards a bottom-up approach for artificial cells, only the recent years showed an active effort by governmental institutions to coordinate and align research groups in a defined direction [15].

5.1 MAXSYNBIO

In 2014, a German consortium involving more than 20 laboratories, mainly from the Max Planck Institutes, was founded under the name of MaxSynBio. In their manifesto, they take distance from the American top-down school and its applicative purposes to rediscover the fundamental research on the origin of life and the formulation of the protocell. MaxSynBio doesn't seek the full creation of life from scratch, but rather the recreation of those fundamental processes that define the *proliferom*, the proliferating unit. The *proliferom* is based on two major prerequisites: processes compartmentalization and protein expression. In its work plan, MaxSynBio is trying to build and assemble five elemental modules for energy, metabolism, growth, signaling/mobility and division. To this end, it proposes the development of a computer-aided design based on different scales to hierarchically assemble synthetic systems. Also, MaxSynBio highlights the importance of solving ethical and epistemological challenges arisen by synthetic life in the scientific and societal environments. In general, the research of this consortium is highly fundamental, with a focus on spatial organization, such as volume control and cellular division [16]. By emphasizing the compartmentalization, MaxSynBio envisions an idea of artificial cell that recalls the eukaryotic cell [11].

5.2 SYNTHETIC CELL INITIATIVE

The European community of Synthetic Cell Initiative was born in 2015 with founders coming from The Netherlands, Germany, France and United Kingdom. It consists today of people from 18 European countries and Israeli laboratories. According to their predictions, artificial cells might be achieved in the next two decades and this will have great impacts in the short and long term. Besides fundamental knowledge, the consortium is looking forward to a broad spectrum of applications: from smart-drugs delivery to new materials, from biosensors to sustainable fuels, food production and many more. Its 20-years-long work plan is divided in three stages. Short-term objectives from the first 5 years concern the bottom-up reconstitution of molecular systems to make up functional modules for metabolism, energy conversion, growth and division. These will also serve as bases for applications in drug screening and drug delivery, biomaterials and energy production. Within 10 years, medium-term objectives focus on the integration of functional modules in the autonomously replicating cells, still with direct spin-offs in biotechnological applications. By the 20th year of the project, long-term objectives involve the study of synthetic multicellular tissues towards a human-cell model to expand the possibilities of regenerative medicine. Together, the initiative highlights the unique role of Europe as a pioneer in the bottom-up approach and on all the side changes that will influence society and industry in the years to come.

5.3 BASYC

In 2017 at the Dutch national consortium called BaSyC (Building a Synthetic Cell) was founded by 6 institutes in the fields of physics, chemistry and biology. BaSyC's work plan aims at tackling the artificial cell from a multifaceted perspective, ranging from theoretical design to the integration of modules, up to the ethics and the public debate behind this challenge. Last year, the Future Panel on Synthetic Life was initiated to face the societal issues of artificial cells. They stress the importance of giving social science and humanities a relevant role to guide a dialogue between society, scientific community, governments and corporates in order to develop the artificial cell field in a more democratic and sustainable way [17].

5.4 BUILD-A-CELL

In the same year as BaSyC, United States came up with the open community of Build-A-Cell. In its manifesto, Build-A-Cell resolves to use the bottom-up approach to develop highly controllable synthetic systems. They hypothesize that a forward engineered biological system will look fundamentally different from the ones selected by natural evolution. Hence, evolutionary concepts like fitness and redundancy will let other qualities go ahead, such as modularity, modellability and simplicity. In general, Build-A-Cell draws inspiration from IT operative systems to create a bio-engineering platform able to promote reliable implementation, sharing and integration of parts, with a special focus on biotechnological applications.

6. TODAY'S PIONEERS

Nowadays, cut-edge research is being carried out all over the world. In the following section, a pinch of the most interesting advances is reported.

6.1 CELLULAR COMMUNICATION AND SIGNALING

At the Imperial College of London Oscar Ces and colleagues used a mutant channel MscL that is chemically activated to create a communication network between linked droplets [18]. In collaboration with Y. Elani, they created a lactose detector with a nested structure, using a human cancer cell as organelle to release glucose subunits for further detection [19]. Recently, the group achieved a signal transmission between nested liposomes functionalized with channel proteins [20]. They are also developing laser-assisted membrane manipulation methods, the optical traps, to drive precise vesicle fusion [21]. Kate Adamala from Build-A-Cell worked on fusion of compartmentalized transcriptional and translational machineries from mammals, resulting in mammalian gene expression, which is normally incompatible in the same compartment.

6.2 PROTOCELLULAR SYSTEMS

At the ESPCI in Paris, Nghe's group is leading theoretical and experimental research on autocatalytic chemical systems. They developed a microfluidics setup to study Darwinian properties of autocatalytic RNA networks [22]. Moreover, the group of Tang from MPI in Dresden demonstrated that coacervates can support ribozymes activity and they can selectively retain long RNA molecules at the expense of shorter ones.

6.3 ENERGY CONVERSION AND METABOLISM

One of the most exciting examples is dated 2018, from the group of Shin at Sogang University of Seoul. A GUV was provided with artificial organelles, consisting of SUVs embedding ATP-synthetases and two different photoconverters for production of protonmotive force (PMF): photosystem II and proteorhodopsin, sensitive to red/blue and green light, respectively. Since proteorhodopsin is able to invert the proton flux under high gradient conditions, hence dissipating the PMF, it was possible to switch on and off ATP production using 2 different wavelengths. Finally, ATP production was coupled to actin polymerization inside the GUV, showing morphological alterations [23] (Fig. 1).

Mavelli's group from University of Bari created a hybrid system by encapsulating chromatophores (bacterial photosynthetic organelles) inside GUVs and obtained a light-driven transcription using a DNA template [24]. The group of Tobias Erb from MaxSynBio integrated thylakoids from spinach in a droplet emulsion with the 16 enzymes of the artificial CETCH pathway for CO_2-fixation, demonstrating the light-dependent carbon fixation activity of this hybrid cell [25] (Fig. 2). Notably, the CETCH cycle was developed *in vitro* by the same group in 2016: it constitutes the 7th CO_2 fixation pathway and it is the first cycle not being naturally evolved, with enzymes belonging to 9 different organisms from all 3 domains of life [26]. Erb's group is continuing to engineer new synthetic CO_2 fixation pathways *in vitro*, such as the TaCo pathway, to overcome the bottlenecks found in nature [27].

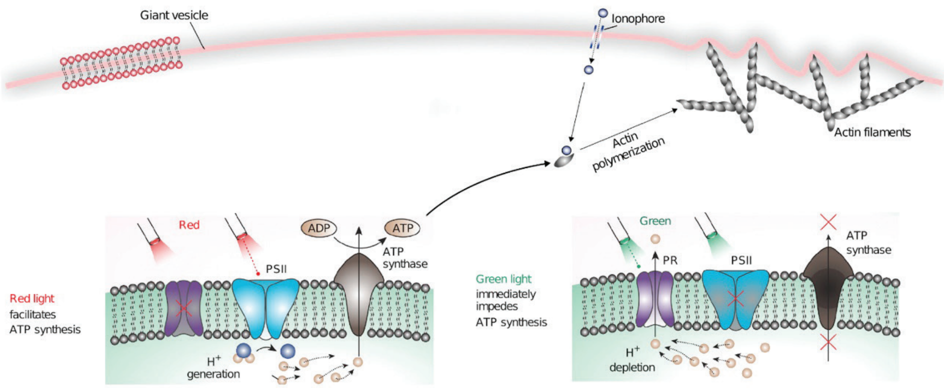

FIG. 1 Photosynthetic artificial organelles sustain and control ATP-dependent reactions in a protocellular system (2018) [23]. Adapted from Lee, K.Y. *et al.*

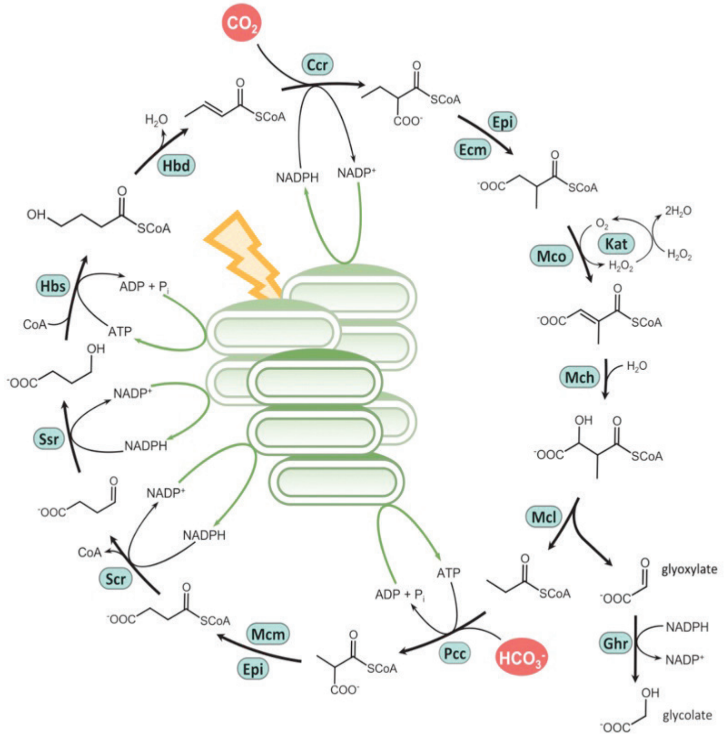

FIG. 2 Light-powered CO2 fixation in a chloroplast mimic with natural and synthetic parts (2020). Adapted from Miller, T.E. *et al*.

6.4 CELL CYCLE

In the Basyc consortium, the group of Danelon from TU Delft has demonstrated the self-replication of phage genetic elements inside liposomes using a PURE system in 2018 [28]. Recently, the group is focusing on liposome growth and division with the bacterial systems Min and Fts, studying protein gradient oscillations and shape deformation of vesicles [29, 30]. Moreover, they expressed a lipid anabolic pathway with the PURE system inside liposomes, putting the bases for a self-sustaining vesicle. The pathway was encoded by 7 different genes and the synthesized lipids were shown to incorporate into the liposome. Besides genetic control, the enzyme PssA showed allosteric feedback regulation from its metabolite, providing a homeostatic mechanism for the membrane lipid composition [31]. Finally, the group is also trying to regenerate the PURE system in liposomes, moving towards a self-sustaining system [32].

Recently, the group of Mutschler from MaxSynBio demonstrated the replication of a 116 kbp multipartite genome starting from a modified PURE system. This genome exceeds both the size of the predicted minimal self-replicable genome and the size of the small *Nasuia deltocephalinicola*. They also detected expression of almost all translation factors, often at a higher concentration than the initial one provided in the PURE set [33].

A spontaneous GUV division process was obtained by the group of Lipowsky from MaxSynBio, exploiting the reversible binding of proteins to functionalized lipids in the outer layer. Interestingly, the process was not due to surface overcrowding [34].

At Wageningen University, the group of van der Oost, member of BaSyC, is collaborating with TU Delft and the AMOLF Institute to study a way to control the synthetic cell cycle. To this end, growth, replication and division must be strictly interconnected. Inspired by bacterial models, this collaboration works towards the design of control modules to couple genome replication and cell division to cell growth [35].

6.5 INTEGRATED MODULES

Another group from Basyc, led by Poolman at the University of Groningen, focuses on minimal metabolism [36] and physicochemical homeostasis [37]. Recently, the group reconstituted the arginine deiminase pathway inside liposomes to produce ATP. The pathway is composed of 4 proteins including the membrane transporter ArcD. ArcD exchanges arginine (the substrate) with ornithine (the end product) in a stoichiometric way. With its antiport activity (substrate in – end product out), this protein keeps the system in a far-from-equilibrium state, until the produced ATP saturates the liposome. To overcome this bottleneck, the group embedded another membrane transporter, OpuA. This transporter is activated under high osmotic stress (such as when there is a big difference in salt concentration between the inside and the outside of the compartment) and uses ATP to import a specific solute to oppose the osmotic stress. The study showed that linking the two modules improved the internal condition for both. Interestingly, ArcD and OpuA were integrated with a method that could not guarantee the right orientation in the membrane, but they only worked in the desired direction thanks to the chemical gradients (i.e. arginine outside and ornithine inside for ArcD and ATP inside for OpuA). This work shows one of the most advanced bottom-up functional reconstitution to date [38] (Fig. 3).

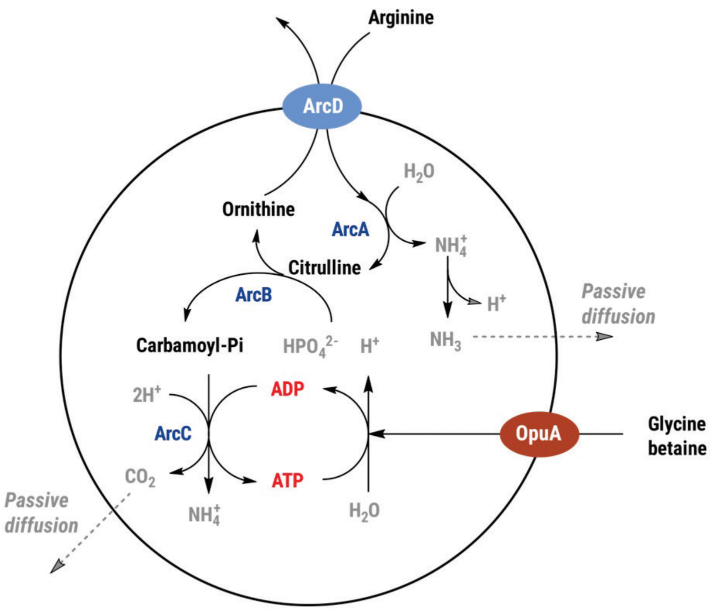

FIG. 3 Physicochemical considerations for bottom-up synthetic biology (2019) [37]. Adapted from Smigiel, W.M. *et al.*

7. DIFFERENT PERSPECTIVES

The future of artificial cells is still a source of debate. Not only which purpose they will serve, but also what they will look like and how they will be built are imagined in a variety of ways.

From MaxSynBio, the biophysicist Spatz devises the development of an artificial cell in a eukaryote-like fashion: the final synthetic cell will eventually be more of a container for other individual modules, each with its vesicle and shape. In such way it would be possible to exploit the potential of modularity and avoid undesired mixes of buffers from different modules [39].

Different perspectives come from the group of Danelon, from TU Delft. They suggest that evolution might not only be an emerging property of assembled cells, but rather the funding principle by which artificial life is obtained and defined. Hence, they envision a semi-rational evolutionary process, opposed to the conventional fully-rational design. This strategy would not provide a precise cell composition, but rather an operative definition for the artificial cell as an outcome of an evolutionary process. Evolution will then turn from "a property" into "the property" on the empirical aspect. Danelon's group anticipates several experimental ways to carry out a high-throughput evolution of both synthetic cells and single modules.

While at the beginning direct evolution of modules would require breaking the vesicles, a continuous system will later guarantee heredity and physical continuity to the genetic elements. This could be obtained first with a mechanical intervention and finally with a synthetic division module. In general, this approach would allow a gradual decrease in the complexity of the system as the evolution proceeds, with each evolution cycle being based on two steps: genetic diversification and phenotype interrogation. Genetic diversification would start with large mutations in random regions (such as recombination events and error-prone DNA replications) to eventually narrow down to site-specific mutations (such as CRISPR/Cas base editing). Phenotype interrogation, instead, can be carried out either with screening methods or with autonomous selection. In the first case, vesicles are sorted with FACS (fluorescence-activated cell sorting) or with the more advanced IACS (intelligent image-activated cell sorting), which could rely on unsupervised machine learning for an open-ended evolution. Instead, autonomous selection can be obtained by retaining vesicles that expose a desired molecule or by selecting for the fittest vesicles once they achieve a functional cell cycle. The outcomes of this semi-rational approach strongly depend on the experimental setup, Danelon's group argues. Hence, it might not be insightful for the origin of the first protocells, but it will strengthen the concept of life as evolution [5].

CONCLUSIONS / CONCLUSIONI

This article followed the path of artificial cells, showing that a new research field, seeking the emergence of life *in vitro*, emerged itself from an interdisciplinary background in the last twenty years. Networks are blooming, especially in Europe, proving the effort of the scientific community to coordinate different disciplines. However, this is not completely true when we take a look at the broader community of synthetic biologists. Albeit top-down and bottom-up approach share a common goal, it is interesting to observe how the two constitute parallel narrations, without a clear acknowledgement of each other [1, 3]. This has been explained with a spatial reason: top-down research is often carried out in life science laboratories, while bottom-up research is subject of physics and chemistry groups. In many institutes, such fields are split in different departments and buildings, impeding close collaborations [2]. Other possible factors might be at fault for this scenario: before the birth of consortia, research could have relied on different funding programs that didn't allow fulfilling collaborations between distant disciplines. Otherwise, the methodological diversity of the two approaches could have confined scientific knowledge to niche journals that were not shared. Nevertheless, specific journals for synthetic biology have been founded and other journals are so influent that they reach both communities. Eventually, different "macromolecules of interest" could dictate the partition, as the top-down school works on DNA, while most of bottom-up research focuses solely on protein reconstitution, bypassing the genetic side. This example shows that perhaps the concept of synthetic biology is too blurred to indicate one definite discipline and the term itself tend to be overused due to its appeal. Nonetheless, it is exciting to see how the awareness is growing and new communities are trying to reduce the gap between the two sides of the coin. Several strategies can be explored by consortia: prioritizing the cytoskeleton rather than the metabolism or relying on assisted mechanical division instead of a genetic module. It will be intriguing to see which strategy will be the best to guarantee the functioning of several modules: either a cytosolic coexistence, like in prokaryotes, or a eukaryotic compartmentalization. Ultimately, we will see if a fully-rational design can unveil the deepest mechanisms of life or if a semi-rational evolution will leave synthetic life with a pinch of ineffable truth.

Questo articolo ripercorre la storia delle cellule artificiali, mostrando come un nuovo campo della scienza, incentrato sull'emergenza della vita *in vitro*, è emerso esso stesso da un background interdisciplinare negli ultimi vent'anni. Nuovi network stanno sbocciando, in particolare in Europa, a prova degli sforzi della comunità scientifica per coordinare discipline differenti. Tuttavia, non si può dire lo stesso quando guardiamo la più ampia comunità di biologi sintetici. Sebbene gli approcci top-down e bottom-up condividano uno scopo comune, è interessante osservare come i due costituiscano narrazioni parallele, senza un chiaro riconoscimento reciproco [1, 3]. Questo aspetto è stato spiegato in precedenza prendendo in considerazione fattori fisici e professionali: la ricerca top-down è spesso materia di laboratori di scienze biologiche, mentre quella bottom-up di gruppi di chimica e fisica. In molti istituti queste discipline sono collocate in sedi e dipartimenti diversi, rendendo più difficili strette collaborazioni [2]. Altre cause potrebbero avere un ruolo in questo scenario: prima della nascita dei consorzi, le ricerche sarebbero potute dipendere da programmi di finanziamento che non permettevano floride collaborazioni tra discipline così distanti. Altrimenti, la diversità metodologica dei due approcci avrebbe potuto segregarne i progressi in riviste scientifiche di nicchia non condivise. Ad ogni modo, sono state fondate riviste specifiche per la biologia sintetica, mentre altre sono così influenti da raggiungere entrambi gli ambienti. Infine, differenti "molecole di interesse" potrebbero aver dettato questa partizione, poiché la scuola top-down lavora sul DNA, mentre gran parte della ricerca bottom-up si concentra sulla sola ricostituzione di proteine *in vitro*, aggirando gli aspetti genetici. Questo esempio dimostra che forse il concetto di biologia sintetica è troppo sfumato per indicare una disciplina ben definita e che il termine stesso rischia di essere abusato per il suo appeal. Nonostante ciò, è emozionante vedere come la consapevolezza stia crescendo e nuove comunità stiano cercando di ridurre il divario tra le due facce della medaglia. Diverse strade potranno essere esplorate dai consorzi: per esempio, dare la priorità al citoscheletro piuttosto che al metabolismo o fare affidamento su una divisione meccanica assistita piuttosto che su un modulo genetico. Sarà affascinante vedere quale sarà la strategia migliore per garantire il funzionamento di numerosi moduli: una coesistenza citosolica, come nei procarioti, o una compartimentalizzazione eucariotica. In definitiva, vedremo se un design completamente razionale potrà svelare i più profondi meccanismi della vita o se l'evoluzione semi-razionale lascerà la vita sintetica con un pizzico di ineffabile verità.

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NEW FRONTIERS IN GLOBAL HEALTH

ONE HEALTH, ECO HEALTH AND PLANETARY HEALTH

LUCA REGAZZI

L'approccio alla salute globale si è sviluppato nel tempo per includere una serie di interazioni naturali che sono emerse in modo drammatico negli ultimi due decenni. Sono stati teorizzati diversi approcci olistici interdisciplinari, tra i quali i più rilevanti sono la One Health, la Eco Health e la Planetary Health. Il concetto olistico di One Health amplia la visione tradizionale della sanità pubblica basata sulla salute umana e si concentra sulle connessioni tra salute umana e salute animale, con una minore attenzione all'ecosistema nel suo insieme. Questo approccio ha ricevuto numerose adesioni a livello accademico, trovando purtroppo conferma nelle numerose zoonosi trasmesse dal mondo animale all'uomo, come le epidemie di Ebola, Zika, SARS, MERS, influenza aviaria del Nilo occidentale, per finire con SARS-CoV-2.
L'approccio Eco Health, invece, recupera una parte dei sistemi tralasciati dal precedente, puntando maggiormente sull'aspetto della biodiversità, con enfasi su tutte le creature viventi, inclusi insetti, organismi unicellulari, batteri e virus. In altre parole, evidenzia la necessità di considerare l'ecosistema nel suo insieme per riuscire a controllare le minacce globali presenti e future per l'umanità.
Infine, l'approccio Planetary Health è più antropocentrico e si concentra sulla promozione del benessere dell'umanità in un contesto di prosperità dei sistemi naturali da cui essa dipende.
Nonostante molte differenze, i tre approcci hanno il potenziale per essere integrati in una visione completa della salute umana, animale ed ecologica e questa unificazione non è mai stata così urgente come in questi tempi di pandemia di COVID-19.

The approach to Global Health has developed over time to include a series of natural interactions that have been dramatically emerging over the last two decades. Several interdisciplinary holistic approaches have been theorized, among which the most relevant are the One Health, the Eco Health and the Planetary Health approach.
The holistic concept of One Health expands the traditional view of Public Health based on human health and focuses on the connections between human health and animal health, with less attention to the ecosystem as a whole. This approach has received numerous adhesions at the academic level, unfortunately finding confirmation in the numerous zoonoses transmitted from the animal world to mankind, such as the epidemics of Ebola, Zika, SARS, MERS, West Nile avian flu, ending with SARS-CoV 2.

On the other hand, the Eco Health approach recovers part of the systems left out from the previous one, focusing more on the aspect of biodiversity, with emphasis on all living creatures, including insects, unicellular organisms, bacteria and viruses. In other words, it pinpoints the need to consider the ecosystem as a whole in order to be successful in controlling present and future global threats to humanity.

Finally, the Planetary Health approach is more anthropocentric and focuses on promoting the well-being of mankind within a context of prosperity of the natural systems on which it depends. Despite many differences, the three approaches have the potential to be integrated into a comprehensive view of human, animal and ecological health and this unification has never been as urgent as it is in these times of COVID-19 pandemic.

PREFAZIONE

Devo confessare che prima della lettura dell'elaborato di Luca Regazzi ero poco informato sugli approcci per il miglioramento della salute umana proposti dai tre consorzi in oggetto: *One Health, Ecosystem Health e Planetary Health*. Tali approcci sono stati molto ben analizzati e discussi nell'elaborato medesimo. Sollecitato dallo scritto, ho visitato i siti web dei consorzi che, in modo simile tra loro, riuniscono istituzioni governative e non governative, università e singoli individui, che hanno il comune obiettivo di sensibilizzare istituzioni e opinione pubblica sull'evidenza che la salute umana è indissolubilmente legata a quella delle altre specie animali e dell'ambiente e, in senso più ampio, al benessere dell'intero pianeta.

La lettura dell'elaborato e il successivo approfondimento dell'argomento mi hanno permesso di cogliere ed apprezzare lo spirito e le motivazioni che hanno indotto l'autore a spingersi in una disamina sistematica degli elementi comuni e di quelli distintivi delle tre proposte. Da un lato, l'estremo interesse per una tematica che sta assumendo una centralità sempre maggiore nelle nostre vite, inducendo sempre più tangibilmente istituzioni e opinione pubblica a individuare ed applicare procedure che possano consentire alle generazioni future di non subire le drammatiche conseguenze di una gestione spesso scriteriata di ambiente e risorse da parte di chi li ha preceduti. Dall'altro, la percezione che pur partendo da un'analisi condivisa delle criticità, gli obiettivi e i metodi proposti per affrontarle e per trovare una soluzione ai tanti problemi che emergono non solo sono diversi, ma vengono a volte perseguiti in modo autoreferenziale e poco critico, senza tenere adeguatamente conto di quanto gli altri attori che si occupano delle medesime problematiche stanno proponendo.

La vera sfida diventa quindi quella di superare i propri limiti metodologici per sviluppare una modalità condivisa di implementazione concreta di questi approcci integrati. Da qui, la proposta dell'autore di inserire il concetto di "One Health" tra le astrazioni stenografiche del Collegio e la volontà, da un lato, di individuare e descrivere quale sia il denominatore comune tra i tre diversi approcci e, dall'altro, di proporre come i medesimi potrebbero superare le loro barriere ed eventualmente integrarsi in framework più strutturati, quale quello dei *Sustainable Development Goals* proposti dalle Nazioni Unite.

Secondo l'autore, ciò che maggiormente accomuna i tre consorzi è il tentativo di proporre un approccio interdisciplinare e forse, in un futuro prossimo, transdisciplinare al miglioramento della salute umana. A tale riguardo, non sorprende che questa modalità abbia suscitato l'interesse di un brillante allievo del Collegio Superiore, istituzione che da sempre ha basato la trasmissione del sapere ai propri allievi su questi principi. E sembra paradossale che l'apparente impermeabilità tra i tre consorzi emerga proprio mentre i medesimi propongono approcci volti ad abbattere i compartimenti disciplinari.

Credo quindi che l'elaborato di Luca Regazzi non solo costituisca un invito a pensare la salute come un problema globale e a perseguire un approccio disciplinare integrato al suo miglioramento, ma rappresenti anche un monito a farlo con la piena consapevolezza che per raggiungere gli obiettivi proposti è necessario che i diversi attori in gioco agiscano in maniera coerente e condivisa.

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INTRODUCTION

Over the last decades, the idea of a connection between human health and animal/ecosystemic health has gained an ever increasing momentum. Several holistic and interdisciplinary approaches have been proposed that work at the human-animal-environment interface in order to safeguard health, among which the most influential are One Health, Eco Health and Planetary Health. From the outside, these concepts might be perceived as relatively synonymous, as they all assume that humans and other living beings share the same planet, and with it the same environmental challenges and infectious agents, as well as other factors influencing physical and possibly mental health [1]. However, while presenting several overlaps, these concepts also differ significantly between them.

A growing need has emerged for a united framework to address the global health challenges of our times, especially in the light of the recent COVID-19 pandemic. For this reason, since there are no agreed definitions of any of these three approaches, several attempts have been made to identify the core aspects of each of these [2, 3], so as to find the common ground on which they can be united and to identify the differences that must be synthesized and overcome. As a matter of fact, no synthesis can be found if these approaches are not clearly defined beforehand in terms of their peculiarities, similarities and differences, given that clear conceptual definitions are the backbone of scientifically sound endeavours [4].

Over the last few years, there has been an effort to combine One Health and Eco Health [5, 6], but this attempt has not involved Planetary Health, which instead has been proposed as an alternative to the other two [7]. The aim of this work is to address the lack of integration between these three approaches, providing a deeper analysis of the peculiarities of each approach and of the similarities and differences between them, to develop a united perspective, without losing the added value that lies in their differences.

THE ONE HEALTH APPROACH

One Health is defined by the One Health Commission as “the collaborative effort of multiple health science professions, along with their related disciplines and institutions – working locally, nationally and globally – to achieve optimal health for people, pets, wildlife, plants and our environment” [8], while the One Health Global Network defines the One Health approach as aimed to “improve health and well-being through risk prevention and mitigation of the effects of crises that originate at the interface between humans, animals and their different environments" [9].

Both definitions seem to implicate a 'whole society' approach which entails the collaboration among all health sciences and their related disciplines to improve health at all levels. While the original approach was mainly focused on human and animal health, there has been a progressive shift towards the inclusion of issues related to biodiversity, ecology, agricultural systems, climate change and social sciences in the sphere of interest of One Health [10]. Therefore, in its narrowest description One Health appears to be the combination of public health and veterinary medicine [1, 11], while in its broader conception this approach includes a wide variety of disciplines from all fields, such as ecology, environmental health, veterinary medicine, human medicine, microbiology, public health, global health and health economics [12].

The narrow vision of One Health is the oldest and originated from what was previously called "One Medicine", an approach primarily developed by doctors and veterinarians [13] and very much focused on conventional medical issues [1]. The term "One Medicine" was then perceived as too limiting, as the health approach was expanded to include public health and ecology issues [12, 14, 15], particularly after the introduction of the Manhattan Principles at the "Building Interdisciplinary Bridges to Health in a Globalized World" symposium at Rockefeller University in 2004 [1, 15, 16]. A schematic representation of the conceptual evolution of One Health is shown in Fig. 1.

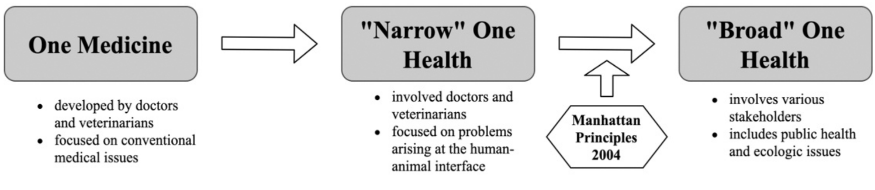

FIG. 1 Schematic representation of the conceptual evolution of One Health, from the narrower idea of One Medicine to that of One Health intended in a broader sense. One Medicine was developed by doctors and veterinarians and focused on conventional medical and veterinary issues. The first "narrow" conceptualization of One Health also involved mainly doctors and veterinarians, but focused on problems arising at the human-animal interface. Finally, the "broad" view of One Health introduced with the Manhattan Principles involves a wider range of stakeholders and includes both public health and ecologic issues.

THE MANHATTAN PRINCIPLES

According to the Manhattan Principles, to win the disease battles of the 21st Century while ensuring the biological integrity of the Earth for future generations, interdisciplinary and cross-sectoral approaches are needed for disease prevention, surveillance, monitoring, control and mitigation as well as for environmental conservation [17].

According to these 12 principles, there is a pressing need to acknowledge the essential link between human, domestic animal and wildlife health and the threat disease poses to people, to their food supplies and economies, and to biodiversity (Principle 1). Similarly, it must be acknowledged that decisions regarding land and water use have real implications for health (Principle 2) and that human health programs can greatly contribute to conservation efforts (Principle 4). Consequently, wildlife health science should be included as an essential component of global health programs (Principle 3) and opportunities should be sought to fully integrate biodiversity conservation perspectives and human needs when developing solutions to infectious disease threats (Principle 6). Adaptive, holistic and forward-looking approaches must be devised for the prevention, surveillance, monitoring, control and mitigation of emerging and resurging diseases (Principle 5), including a better regulation of international live wildlife and bushmeat trade (Principle 7) and a restriction of mass culling of free-ranging wildlife species for disease control to situations where it is really necessary (Principle 8). These objectives imply higher investments in the global human and animal health infrastructure (Principle 9), in global human and animal health surveillance networks (Principle 11) and in education and awareness programs (Principle 12), without forgetting the need to form collaborative relationships among governments, local people, and the private and public (i.e. non-profit) sectors to meet the challenges of global health and biodiversity conservation (Principle 10).

As can be seen, some of these principles (3, 7, 8, 9, 11) deal with the narrower view of One Health as the interface between human and animal health, with particular attention to zoonoses. However, most principles (1, 2, 4, 5, 6, 10, 12) take a broader approach to human health within the context of the ecosystem humans live in, showing overlaps with Eco Health.

In fact, these principles represented the first ecological approach to human health and can be considered as the initial foundation of One Health in its broader sense [1, 5]. However, it must be noted that, even in its broader definition, the One Health approach still relates to public human health and animal health affecting human health. Therefore, the individual health of vertebrates is usually the focus, even when ecosystems are included in the model [12]. The main issues addressed by One Health in its broader conception are [18-20]: climate change and environmental pollution; antimicrobial resistance (AMR); zoonotic and vector-borne diseases; nutrition; and animal welfare.

Climate change and environmental pollution can be considered as "threat multipliers", since they affect zoonoses, food safety, vector-borne diseases (e.g. West-Nile virus, malaria, etc.) and non-communicable diseases as well (e.g. asthma, cardiovascular diseases, cancers, etc.) [18-19].

Antimicrobial resistance (AMR) is one of the main topics addressed by One Health and is driven by various phenomena, including: over-prescription or inappropriate prescription of antibiotics in assistance settings (e.g. hospitals) and by general practitioners; misuse of antibiotics by the general population, because of insufficient health literacy and/or lack of trust in medical guide-lines; overuse of antibiotics for prophylaxis to promote cattle growth (especially in intensive farms), with the consequent spillover of resistant pathogens from animals to humans (and vice versa) [21].

Zoonotic and vector-borne diseases are equally relevant to One Health. The inter-species jump of pathogens is facilitated by prolonged human-animal contact in intensive farms, the exploitation of wildlife for food and recreation, the human and livestock encroachment of forests, the expansion of urban cities and the degradation of rich ecosystems, with the consequent loss of the protective effects of biodiversity (i.e. dilution of potential hosts, obstruction to the spread of vectors).

Nutrition is a very important issue as well as unsafe food is estimated to cause 600 million cases of food-borne diseases annually, with food safety being affected by chemical additives (e.g. pesticides, toxins, etc.) and biological agents (e.g. micro-organisms, parasites, etc.) [22, 23].

Animal welfare, finally, is related with AMR, zoonotic diseases and nutrition, since around 60% of human pathogens are of animal origin and can be exchanged both ways between animals and human. Thus, translocation of exotic species, wildlife trade, mass rearing of animals (as seen during intensification of animal farming) and deforestation are some of the anthropogenic activities that can negatively affect the interface between human health, ecosystem and animal health [24].

Overall, the One Health approach links human, animal and environmental health through multi-sectorial and transdisciplinary approaches, tackling global health issues by prioritising the health of humans and animals, with a particular on infectious diseases control and prevention [15].

THE ECO HEALTH APPROACH

The Eco Health approach has been described as engaging the health of humans, animals and ecosystems as wholes, including in its framework also environmental sustainability and socioeconomic factors [1]. In other words, Eco Health is a systems-based approach to promoting health and well-being with a focus on social and ecological interactions [15].

Compared to One Health, the Eco Health approach emphasizes the role of biodiversity, with a focus on all living creatures, implying that even insects, parasites, single-celled organisms and viruses should be protected because of their inherent value and not just because they are functional to human health [1, 25]. In fact, this approach was designed by disease ecologists working in the field of biodiversity conservation [25] and aims at «sustainable human and animal health and well-being, through healthier ecosystems», in the context of a sustainable and equitable development [1, 26].

The EcoHealth Journal website defines the Eco Health approach as "committed to promoting the health of humans, animals and ecosystems and conducting research that recognizes the inextricable links between the health of all species and their environment" with the "fundamental principle [...] that health and well-being cannot be sustained on an impoverished, polluted and socially unstable planet" [9].

This approach includes more social sciences and humanities than One Health (especially when intended in its narrower definition) and involves various disciplines, such as human medicine, veterinary medicine, public health, rural and urban development and planning and ecosystem conservation and management [27]. Since it considers the health of human individuals not only in the context of their natural but also of their social environment, it fosters the participation of communities to include various social dimensions in the analysis and solution of given health issues [15]. The consideration of health or illness as more than just the result of the cumulative effects of independent social or environmental determinants is a cornerstone of the approach, as it recognizes that health and well-being are the result of complex and dynamic interactions between human, social, economic and environmental determinants, while the conditions of ecosystems are also affected by the social and economic activities of people [2].

Of the three approaches analyzed in this work, Eco Health is probably the least well-defined. However, the International Development Research Center (IDRC), a Canadian public corporation dedicated to supporting developing countries through the funding and advancement of their own researches, has identified three methodological pillars (in 1994) and six key principles (in 2012) of Eco Health [28], as shown in Fig. 2.

THE THREE METHODOLOGICAL PILLARS OF ECO HEALTH

The three methodological pillars of Eco Health are transdisciplinarity, participation and equity [29]. Transdisciplinarity implies an inclusive vision of ecosystem-related health problems and requires transdisciplinary communication among researchers, community representatives, and decision-makers. Participation refers to the aim of achieving consensus and cooperation, not only within groups (community, scientists, decision-makers), but also among them, to ensure that all stakeholders feel their voices heard. Equity, finally, implicates the analysis of the respective roles of men and women and of various social groups, to acknowledge how different people might be impacted by any decision.

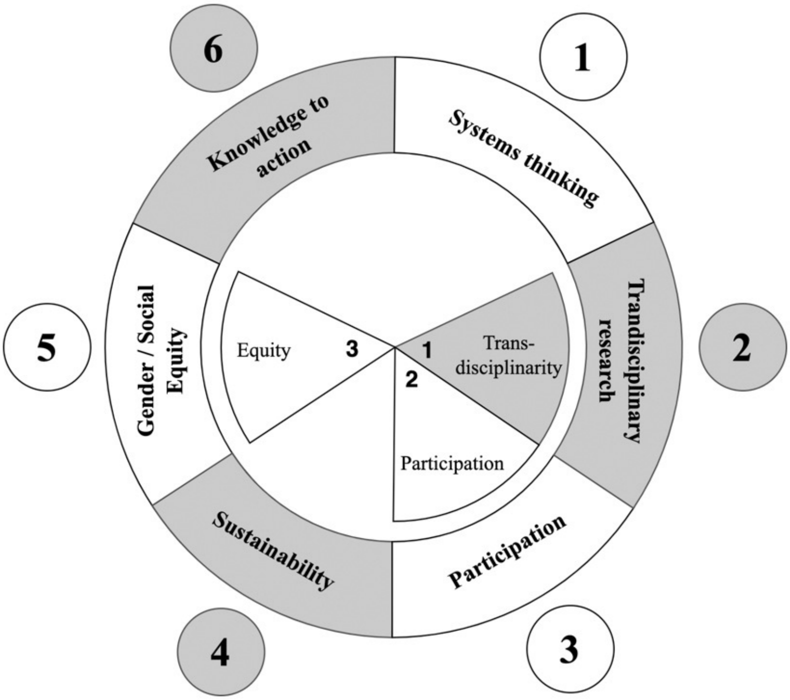

FIG. 2 Schematic representation of the intersection among the three pillars and the six key principles of Eco Health. The three pillars are: Transdisciplinarity, Participation and Equity. The six key principles are: Systems thinking, Transdisciplinar research, Participation, Sustainability, Gender / Social Equity, Knowledge to action.

THE SIX KEY PRINCIPLES OF ECO HEALTH

The six key principles of Eco Health incorporate the three above-mentioned pillars and add three new items. These principles are systems thinking, transdisciplinary research (i.e. Pillar 1), participation (i.e. Pillar 2), sustainability, gender and social equality (i.e. Pillar 3), and knowledge to action [2]. Systems thinking holds that the component parts of a system can best be understood in the context of their relationships with each other and with other systems, rather than in isolation, focusing on cyclical rather than linear cause and effect relations and examining the linkages and interactions between the elements that make up the system. For this reason, multiple levels of complex interactions have to be considered when approaching systemic health problems. Sustainability implies that research should aim to make ethical, positive, and lasting changes that are environmentally sound, as well as socially acceptable to the target community which must live with that change. The latter aspect is the main reason why Eco Health focuses hugely on participation (key principle 3, pillar 2). Finally, knowledge to action, which refers to the idea that knowledge generated by research must then be used to improve health and well-being through a bettered environment. In other words, Eco Health must not remain a theoretical approach but needs to be applied to practical use cases.

These pillars and key principles provide the context within which human health issues must be addressed and represent the main innovation compared to the One Health approach, while sharing some similarities with the Planetary Health approach. In fact, while the emphasis on sustainability and equity is characteristic of the latter, the main challenges tackled by Eco Health are common to those of One Health, including zoonotic diseases, antimicrobial drug resistance (particularly in food-borne pathogens) and food-borne diseases [25, 28]. However, Eco Health puts a focus also on environmental health more generally, considering the health effects of biodiversity loss, human population growth, climate change, land use and land cover change (e.g. urbanization, intensive agriculture and farming), air quality, water quality, waste management and agriculture-associated problems. Furthermore, Eco Health also takes into account the social and economic aspects of these issues and the impacts of their possible solutions, with special attention to the promotion of equality and to the need for acceptance by the impacted communities [28]. In fact, the knowledge generated by Eco Health research is intended for use by local communities and policymakers especially at local scales [2].

To conclude, the Eco Health approach promotes positive action on the environment that improves community well-being and health, since it recognizes that the economy, the environment, and community needs all affect the health of the ecosystem and that focusing on just one of these factors to the detriment of others might compromise ecosystem sustainability. In this context, it is impossible to improve the environment without considering the human population living in it, with its inherent social, cultural, and economic concerns. Therefore, a sectoral approach is no longer adequate and co-management of the environment and human activity is essential [30].

THE PLANETARY HEALTH APPROACH

The concept of Planetary Health was developed in 2015 by the Rockefeller Foundation-Lancet Commission on Planetary Health and was defined as «the achievement of the highest attainable level of health, well-being and equity worldwide through judicious attention to the human systems - political, economic and social - that shape the future of humanity and the Earth's natural systems that define the safe environmental limits within which humanity can thrive» or, in simpler words, «the health of human civilisation and the state of the natural systems on which it depends» [1, 7, 15].

In recent years, given its multiple overlapping principles and ideas with both One Health and Eco Health [15], this approach has been proposed as an alternative to both of them, even though it appears to be less interdisciplinary than the others and focuses primarily on human health, with the environment being considered as instrumental to it [1]. In other words, Planetary Health can be seen as the natural successor to public and global health, as it expands the global health focus on improving health and achieving equity, by incorporating the concept of sustainability into the framework [15].

The Planetary Health approach values humans more than other animals or other members of their ecosystems and focuses on mitigating and responding to threats to human health and well-being, within the context of the sustainability of the entire human civilization [31]. In fact, the Commission on Planetary Health acknowledges the importance of biodiversity as a core element of the natural systems on which human society depends, without discussing the intrinsic values of the ecosystems and of non-human beings, so that this approach looks exceptionally anthropocentric and only emphasizes the importance of human health outcomes [31]. Similarly, differently from the One Health and Eco Health approaches, animal health and animal welfare in the interest of animals are not mentioned because they are perceived as relevant only in terms of potential disease transmission to humans and in terms of capacity of food production [1].

The Planetary Health approach originated from the acknowledgement that current generations of humans have been mortgaging the health of future generations to realise economic and development gains in the present. As a matter of fact, present highly inequitable and unsustainable patterns of resource consumption together with population growth are fuelling changes to the environment (such as over-exploitation of fisheries, biodiversity loss, water scarcity, land degradation, ocean acidification and climatic change) whose health effects are expected to pose serious challenges to the global health gains of the past several decades [7, 32]. Consequently, according to the Planetary Health approach, several steps should be taken to redefine prosperity focusing on the enhancement of quality of life and to deliver improved health for all, while respecting the integrity of natural systems [7].

Resilient food and agricultural systems should be created to address both undernutrition and overnutrition, reduce waste, diversify diets, and minimise environmental damage, as urged also by the EAT-Lancet Commission on healthy diets from sustainable food systems [33]. In parallel, the economy should be transformed to support planetary health, by reducing waste through the creation of products that are more durable and require less energy and materials to manufacture than those often produced at present and by incentivising recycling, reuse, and repair.

Natural systems should be protected, with an indirect reduction in human disease risk by promoting ecosystem health and defending biodiversity. At the same time, the urban environment should be improved through reduced air pollution, increased physical activity, provision of green space, and urban planning to decrease the magnitude of urban heat islands.

Such actions should be undertaken by means of a transdisciplinary approach to research and implementation, involving health professionals, researchers, policy-makers and the civil society [7].

In other words, from an operational point of view, Planetary Health focuses more on policy responses to climate change, ocean acidification, freshwater usage, land use and soil erosion, pollutants and the loss of biodiversity and less on health issues arising at the human-animal interface, such as the control and prevention of zoonotic transmission between humans and animals. At the same time, in Planetary Health a great importance is given to human effects on the environment, looking at factors that can be modified in order to mitigate negative effects, such as land consumption, population growth, urbanisation and technological advancements. Furthermore, Planetary Health has an increased focus on public and global policy, proposing itself as an implementer and integrator of the objectives defined by the Sustainable Development Goals (SDGs) framework [7], as discussed later.

As for the interdisciplinarity, in its narrower conception Planetary Health only involves human health professionals, public health professionals and policy makers, while in the broader definition proposed by the Rockefeller Foundation-Lancet Commission on Planetary Health this approach involves a wide spectrum of scientific disciplines other than human medicine and public health, such as ecology and other environmental sciences (with a focus on climate change and biodiversity loss), economics, energy, agricultural and marine sciences (with a focus food production from plant and animal sources) [1, 7, 31]. From this point of view, in its broader sense, Planetary Health's methods are similar to those of One Health and Eco Health. However, the core value of the Planetary Health approach remains the health of living and future human generations, at the individual, community and population level [1, 7], with a significant stress on equity in health and on sustainability in terms natural resources and biodiversity conservation [1], as it is strongly influenced by the global health framework.

DIFFERENCES AND SIMILARITIES BETWEEN ONE HEALTH, ECO HEALTH AND PLANETARY HEALTH

The three approaches presented in this work certainly have various overlaps and similarities, as shown in Fig. 3. This is especially true for One Health and Eco Health, while Planetary Health appears to differ insofar as how it values humans, animals and ecosystems. In fact, One Health and Eco Health regard humans and animals on the same level, while Planetary Health is more anthropocentric and emphasizes the need for environmental sustainability only as a mean to promote human health on a global scale [1, 34]. Because of their similarities, One Health and Eco Health are often considered as a single concept, despite the existing differences [1, 5, 6, 35]. However, it is generally acknowledged that, while being less supported at official levels, the Eco Health paradigm takes a broader view of public health, linking it to natural resource management within an ecosystem approach to human health and including strong participatory and citizenship components [25, 34]. For this reason, Eco Health might be seen as a bridge between One Health and Planetary Health, despite the existing differences with both of them.

One of the most obvious differences between the three approaches regards the view of health. Planetary health focuses mainly on global health, considering the well-being of the planet as instrumental to human welfare [7, 34]. The other two approaches share a broader perspective: One Health mainly focuses on the interrelation between animal and human health, while Eco Health mainly deals with the relationship between health and ecosystems as wholes [5]. In other words, the One Health approach attributes health to individual bearers while Eco He-

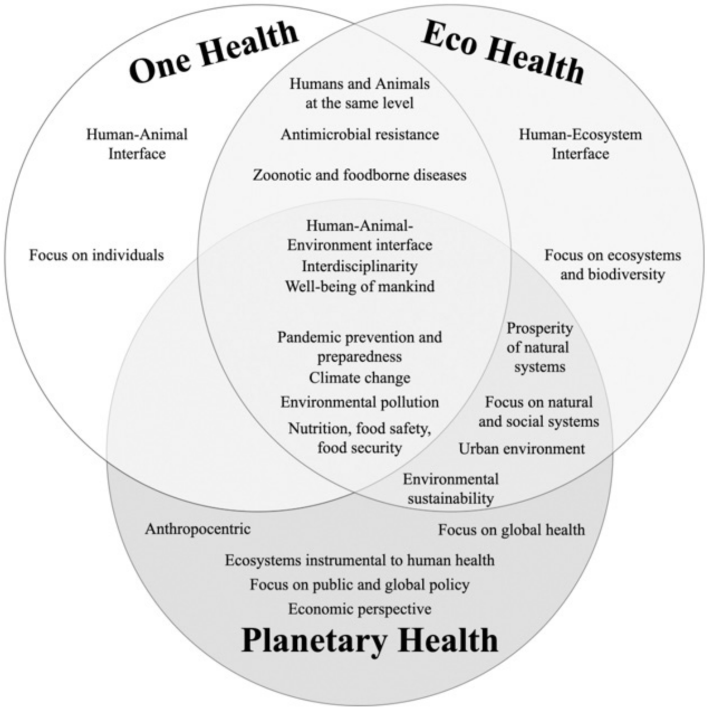

FIG. 3 Venn diagram evidencing similarities and dissimilarities between One Health, Eco Health and Planetary Health. Despite their differences, One Health, Eco Health and Planetary Health share a significant common ground: in their own way, they are all interdisciplinary approaches working at the human-animal-environment interface for the well-being of mankind, addressing themes such as pandemic prevention and preparedness, climate change, environmental pollution and nutrition/food safety/food security. Both One Health and Eco Health consider humans and animals at the same level, addressing also questions related to antimicrobial resistance, zoonoses and foodborne diseases. However, One Health is mainly focused on individuals and concerned with the human-animal interface, while Eco Health is mainly focused on systems and concerned with the human-ecosystem interface. Both Eco Health and Planetary Health focus on natural and social systems, incorporating notions of environmental sustainability and of urban health. However, Planetary Health is more anthropocentric and focused on global health, with a stronger political and economical basis. Overall, a comprehensive approach can be envisioned with Eco Health acting as the bridge between One Health and Planetary Health.

alth attributes health to systems. The view of Planetary Health is more similar to that of Eco Health, insofar as it stresses the importance of natural systems in determining human health. However, a fundamental difference between the two remains, since Planetary Health always considers ecosystemic health as instrumental to human health and not as a value per se [1]. Overall, the differences relating the notion of health might be overcome by considering that these three integrated approaches to health are all motivated by the conviction that human health concerns must be addressed at the interface with the health of other living beings, within their broader natural and social environments (i.e. socio-ecosystem approach), integrating scientific disciplines and combining multi- and cross-disciplinary approaches [1, 25].

In fact, all three approaches are based on inter- or multi-disciplinary research and actions, having stemmed from the understanding that the only way to properly face health issues is with contributions from several disciplines. However, within the same interdisciplinary framework, each approach retains its own peculiarity and focus. Planetary Health particularly emphasizes human health and related research areas, while One Health mainly focuses on human and veterinary medicine [11]. Eco Health, on the other hand, seems to have a wider perspective, embracing contributions from various scientific and socio-economic disciplines [5]. However, it must be noted that the One Health perspective has become wider and wider over the years, developing significant overlaps with Eco Health [10, 12], while also Planetary Health in its broader sense can involve an equally wide variety of disciplines [7].

IS A COMPREHENSIVE APPROACH POSSIBLE?

It is reasonable to believe that the One Health and Eco Health perspectives might be merged and integrated into a single comprehensive approach, as they are not mutually exclusive. Planetary Health, on the other hand, might be harder to incorporate into a merged approach because of its main focus on human health and its instrumental view of non-humans beings and systems [1].

However, while differing for their moral foundation and their vision, the three approaches usually converge towards compatible conclusions, so that a comprehensive approach encompassing all of them should not be ruled out [1, 25, 36]. For example, there are voices arguing for a more thorough and broader approach called One Welfare, which should focus on human, animal and social welfare while promoting the health of the environment [37], while others are calling for a Planetary

One Health approach to better connect global health efforts in disease control and preparedness to larger issues of climate change, equity and sustainability [34].

The need for a comprehensive interdisciplinary approach stressing connections between human, animal and environmental health gained momentum as a response to the steadily increasing number of emerging zoonotic disease outbreaks in recent decades, including the West Nile virus, severe acute respiratory syndrome, Ebola, avian influenza, H1N1 2009 pandemic influenza, and most recently Ebola in West Africa, zika, yellow fever and COVID-19 [34].

In 2019, the founding principles of One Health – the Manhattan Principles – have been reviewed in light of the fundamental changes in terms of climate change and loss of biodiversity undergone by our planet. At the "One Planet, One Health, One Future" convention in Berlin advocates of One Health, Eco Health and Planetary Health have been brought together to join forces. This convention lead to the introduction of the "Berlin Principles on One Health", an update to the Manhattan Principles which addresses pressing current issues, such as ecosystem health, climate change, the spread of pathogens and antimicrobial resistance [16].

THE BERLIN PRINCIPLES

The Berlin Principles are ten principles formulated to overcome the most important systemic policy and societal barriers to tackle increasing health threats at a global scale, thanks to the contribution of a comprehensive approach borrowing ideas from One Health, Eco Health and Planetary Health [16]. According to these principles, there is an urgent need to acknowledge the essential health links between humans and all other living beings (Principle 1), while ensuring the protection of biodiversity, which provides the critical foundational infrastructure of life, health and well-being on our planet (Principles 1, 6). Further actions must be taken to mitigate the impacts of the current climate crisis (Principle 3) and of unrestrained land, air, sea and freshwater use (Principle 4) on the emergence, exacerbation and spread of communicable and non-communicable diseases. At the same time, adaptive, holistic and transdisciplinary approaches must be devised for the detection, prevention, surveillance and mitigation of such diseases, while accounting for harmful economic drivers (Principles 5, 8). Finally, there is a need to create an enabling environment for an holistic vision of health, by means of developing stronger institutions that integrate human, animal and environmental health (Principle 2), increasing cross-sectoral investment in the field (Principle

7), forming participatory, collaborative relationships among supranational bodies, governments, NGOs and local communities (Principle 9) and investing in raising awareness for holistic planetary health approaches among children and adults (Principle 10).

Each one of these principles incorporates some aspects of One Health, Eco Health and Planetary Health, which are so intertwined that the contribution of each approach cannot be easily isolated. A paradigm shift is needed to address the growing disconnection between human health, animal health and environmental/ecosystem health, moving from the current fragmented framework of health governance for human, animals and environment to a more integrated approach. This new approach should de-sectoralize human, animal, plant and ecosystem health and should be based on inputs from all three holistic approaches to health [36].

THE SUSTAINABLE DEVELOPMENT GOALS (SDGS)

According to some authors, the framework of the UN 2030 Agenda for Sustainable Development Goals (SDGs) might represent a political opportunity for integrating the silos of One Health, Eco Health and Planetary Health into a comprehensive approach [15, 36], as shown in Fig. 4.
The Sustainable Development Goals (SDGs) or Global Goals are a collection of 17 global goals designed to be a «blueprint to achieve a better and more sustainable future for all». They were set in 2015 by the United Nations General Assembly and are intended to be achieved by the year 2030, having been included in the UN Agenda 2030 [38]. All Sustainable Development Goals (SDGs) are intertwined and most, if not all, of them have health embedded within them, since SDGs representing human well-being (SDGs 1, 3, 4, 5, 10, 16) are dependent on those that provide the enabling infrastructure for development (SDGs 2, 6, 7, 8, 9, 11, 12) and the supporting natural systems (SDGs 13, 14, 15) [7], as shown in Fig. 5. However, some SDGs have a stronger relation to health than others [36].

SDG 3 is specific for health and requires to *ensure healthy lives and promote well-being for all at all ages*. It is strictly related with urban development (SDG 11), which not only creates job opportunities (SDG 8) and wealth (SDG 1), but also increases disease risk and health inequalities. Unfortunately, current health systems appear to lack an integrated approach to health issues related to the natural and urban environment we live in, while a trandisciplinar collaboration for the allocation and design of urban green spaces is pivotal to improve health.

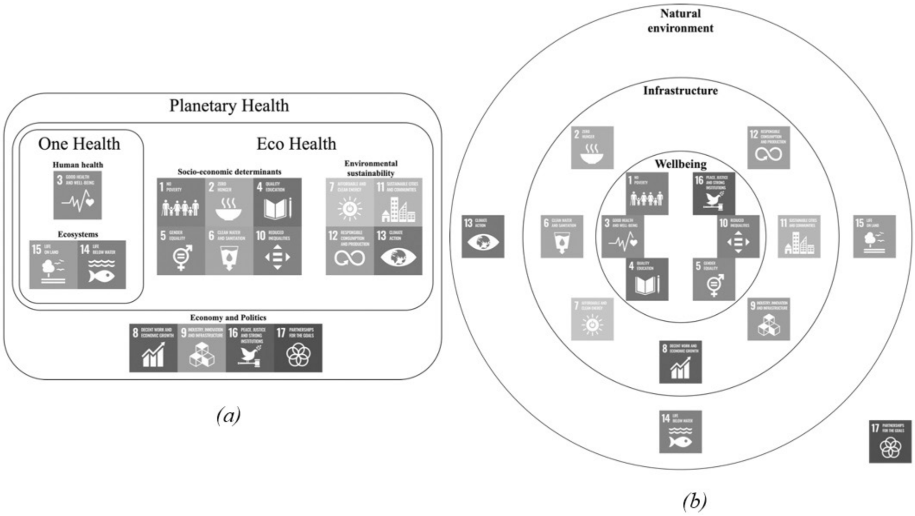

FIG. 4 (**a**) Schematic representation of the intersection between the 17 SDGs and the three approaches of One Health, Eco Health and Planetary Health. When interpreted in the light of the SDGs, One Health in its narrower sense is concerned with human (SDG 3) and ecosystem health (SDGs 14, 15) alone, while Eco Health expands its interest to the socioeconomic determinants of health (SDGs 1, 2, 4, 5, 6, 10) and to environmental sustainability (SDGs 7, 11, 12, 13) and Planetary Health extends its preoccupation even to economical and political factors (SDGs 8, 9, 16, 17). (**b**) Schematic representation of the interdependence between SDGs related to human wellbeing (1, 3, 4, 5, 10, 16) and SDGs related to the social (2, 6, 7, 8, 9, 11, 12) and natural (13, 14, 15) infrastructure that support human health, as adapted from [38] and [34].

SDG 1 (*to end poverty in all its forms*), **SDG 2** (*to attain food security and improved nutrition through sustainable agriculture*) and **SDG 6** (*ensure availability and sustainable management of water and sanitation for all*) are deeply interrelated and have all a strong effect on health. Poverty entails poor housing, lack of food (SGD 2), unsafe water supplies (SDG 6) and lack of healthcare, leading to an unequal burden of disease, with diarrhoeal diseases, tuberculosis, HIV and malaria ranking among the top causes of poverty-linked human deaths. Food security must be attained all over the world to avoid malnutrition, but it must be based on balanced and sustainable diets, to avoid diseases of affluence (e.g. obesity, diabetes) and assure the long-term durability of our food systems. Freshwater quantity and quality are dependent on healthy water ecosystems, so that maintaining healthy freshwater ecosystems is a cost-effective way to improve water quality, biodiversity and human health. SDG 1, 2 and 6 have also a strong link with SDG 4 on education and SDG 5 on gender equality, as poverty, food insecurity and the scarcity of water disproportionately affect children and women.

Finally, given the interdependence between health and natural systems, also **SDG 13** (*take urgent action to combat climate change and its impacts*), **SDG 14** (*conserve and sustainably use oceans, seas and marine environments*) and **SDG 15** (*protect, restore and promote sustainable use of terrestrial ecosystems*) have important implications for health. Through its impact on biodiversity, climate change affects human and animal health both directly and indirectly, causing the emergence and re-emergence of disease. In fact, climate change and biodiversity integrity are two core planetary boundaries through which other natural systems operate and on which our health and existence depend. In fact, biodiversity loss due to intensive agriculture, industrial livestock production, urbanization and over-exploitation of natural resources (e.g. overfishing), can impact health by increasing the likelihood of both communicable diseases (wider vector distribution across fewer species) and non-communicable diseases (reduced food diversity, with increasing reliance on fewer unhealthy foods).

Overall, the SDGs framework is coherent with the underlying principles inspiring the One Health, Eco Health and Planetary Health approaches that: humans must accept that they are a component of the complex and adaptive ecosystems they live in and that their health is directly related to the health of the system; and that humans must recognize their dependence on ecosystem services and their responsibility for the negative environmental impacts caused by their previous, current and future development. For this reason, given its political momentum, the SDGs framework actually provides a unique opportunity for a move towards a more integrated approach to the future health of all through the development of a comprehensive framework for the integrated management of health [7, 36].

Irrespective of the name chosen for the comprehensive approach, advocates from all three approaches need to join to be effective in the policy arena, so as to carry forward the idea that modern public/global health can be addressed only as a composite of human, animal and ecological health. The comprehensive approach must be pragmatic, systems-based, informed by evidence and policy-informing, moving far beyond the simple recognition that many infectious diseases are zoonotic to addressing the many challenges faced by the human civilisation on the planet [15]. This is especially true in the light of the COVID-19 pandemic, which has highlighted the need to promote broader approaches to public and global health. In fact, the pandemic has underscored the irrelevance of the boundaries between One Health, Eco Health and Planetary Health, when faced with the necessity of integrated perspectives within the broader context of the Sutstainable Development Goals (SDGs), with particular attention to climate change, to properly address the impact of emerging infectious diseases and of health threats on economics and society [16, 39-41].

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THE QUEST FOR IMMORTALITY

A FINE LINE BETWEEN LEGEND AND SCIENCE

MARTINA TOMIROTTI

L'*Homo sapiens* ha percorso un lungo viaggio millenario per evolvere nell'uomo del giorno d'oggi, il tortuoso cammino dell'evoluzione ha prodotto numerose culture, tradizioni e religioni, che pur essendo straordinariamente diversificate trovano un filo conduttore nell'incessante ricerca di metodi, fisici o spirituali, per sfuggire alla morte. Dapprima questa fascinazione si manifesta sotto forma di miti e leggende, poi si sviluppa in complesse religioni. L'ambizione dell'uomo presto lo spinge oltre la narrazione fino alla creazione di pozioni ed elisir formulati per ottenere un'immortalità fisica e tangibile, spesso ottenendo il risultato opposto. Se pensiamo al Sacro Graal, alla Pietra Filosofale e all'Elisir di lunga vita sorridiamo sotto i baffi, eppure siamo sicuri di non aver traslato l'essenza di questi miti leggendari nelle nostre routine di bellezza? In questo trattato intraprenderemo un viaggio attraverso i millenni per osservare quali soluzioni sono state proposte dall'uomo per tentare di raggiungere l'immortalità, partendo dalla comparsa dei primi ominidi sulla Terra fino alle ricerche fantascientifiche del giorno d'oggi. Dalla storia alla religione, dall'arte alla scienza, dalle considerazioni etiche a quelle economiche, ci troveremo a ponderare se sconfiggere la morte, un evento *per ora* imprescindibile dalla vita, sia davvero ciò che desideriamo.

Homo sapiens has come a long way through millennia to evolve into modern day man, the winding path of evolution has produced astonishing cultures, traditions that, even though extraordinarily diversified, they find a common thread in the restless research of physical or spiritual methods to escape the grim grasp of death. This fascination first manifested in the form of legends and myths, soon it developed into complex religions. Eventually, man's ambition pushed him to create, other than narrate, potions and elixirs concocted to reach a physical immortality, often achieving the opposite result. If we think about the Holy Grail, the Philosopher's Stone and the Elixir of Long Life we smile to ourselves, but haven't we transferred their essence into our beauty routine? In this chapter we'll wander through a millennia long quest to ponder the human methods to reach immortality, from the first appearance of hominids on Earth to the borderline science fiction research in nowadays laboratories. From history to religion, from art to science, trough ethics and economics, we'll find ourselves questioning if we really desire to defeat death, an event *for now* inescapable.

PREFAZIONE

La prospettiva della morte, e dell'invecchiamento che inevitabilmente vi conduce, è da sempre tematica più che mai critica e dibattuta. Storicamente, una delle reazioni del genere umano è stata la formulazione della nozione di vita dopo la morte, alla quale viene attribuita gran parte del successo di religioni, sette e culti religiosi ufficiali e non. Un altro approccio contempla invece l'adozione di pratiche mentali o fisiche per il prolungamento della vita, addirittura fino all'ipotetico raggiungimento dell'immortalità fisica. Questo è ciò che viene chiamato *prolongevity*. La prolongevità ha una lunga storia e appare in molte culture diverse. Il mondo occidentale contemporaneo non fa eccezione, con svariate tipologie di ricette scientifiche, semiscientifiche o francamente antiscientifiche per aumentare la durata della vita, dal prediligere una certa alimentazione (i *superfoods*!), al non mangiare affatto, o quasi.

Ovunque nel mondo, donne e uomini hanno a lungo nutrito l'ossessione di vivere per sempre, e alcuni ancora la coltivano; ma tutti costoro hanno qualcosa in comune: hanno fallito. Eppure, il sogno dell'eternità non vacilla. In tanti ancora oggi si chiedono se la chiave della loro immortalità non si possa già intravvedere all'orizzonte, nel bacino in continua espansione della conoscenza umana. La scienza moderna ha aperto strade impensabili fino a poco tempo fa per migliorare la salute, prevenire le malattie, prolungare la vita, ritardare l'invecchiamento, e ora i membri dell'*élite* degli ultra-ricchi del pianeta guidati dalla tecnologia stanno adottando nuovi approcci nel tentativo di diventare sempre più longevi, forse quasi immortali. Ma ciò che spesso non viene detto è che la scienza moderna ha anche rivelato il lato più oscuro della longevità: gli inevitabili compromessi fisiologici, il decadimento fisico e mentale, il penultimo tabù che sembra per ora destinato a limitarci.

In questo capitolo, Martina Tomirotti ci propone un avvincente excursus sull'argomento, partendo da una domanda tanto semplice quanto profonda: perché vorremmo essere immortali? Con una panoramica attraverso la storia, l'arte e la religione, vengono presentate le varie risposte che l'essere umano, grazie all'intelletto e al sentimento, ha avvicendato e intrecciato. Si arriva quindi sino all'era moderna e ai punti di vista della scienza che si prefigge di contrastare i processi di invecchiamento, ma che prima di tutto deve ancora fare molta strada per comprenderne a fondo i meccanismi, ancora in parte sconosciuti. Passando quindi dallo stretto legame, talvolta paradossale, che c'è tra scienza e profitto economico, spesso costellato di false promesse, tra considerazioni sociali ed etiche riguardo a ciò che realisticamente possiamo aspettarci o che sarebbe moralmente giusto fare nel futuro, il lettore viene lasciato con una riflessione per nulla banale: vale davvero la pena di rincorrere l'immortalità?

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INTRODUZIONE

I don't want to achieve immortality through my work.
I want to achieve it through not dying.
Woody Allen

Through millennia of history, mankind has always been fascinated with the idea of overcoming death. Humanity's aspiration towards longevity first manifested in legends and myths, soon after it appeared in religion as an attribute of the divinities created. Eventually, men got tired of narrating the perks of immortality and started to concoct the so-called elixir of immortality themselves, often achieving the opposite result.

Although the quest for longevity has indeed been very successful, we have doubled life expectancy since the Industrial Revolution, we haven't reached eternal life yet. Death is still inevitable, and the best shot at immortality is through one's extraordinary work, much to Woody's disappointment. But even after thousands of years of failure, humans haven't given up yet. As the saying goes, *hope springs eternal*.

Proof of this ongoing fascination can be found virtually anywhere, from fine art to poetry and literature to Hollywood movies. Yet this commitment to combating aging is not only found in artistic or intellectual products but also broadcasted on every media platform (TV, social media, advertisement on websites) and supermarket shelves as a plethora of anti-aging cosmetics and supplements. Contrasting aging is so engraved into our society that the ancient and legendary Philosopher's Stone and the Elixir of Long Life have transmuted into the daily creams, oils, vitamins, pills, and whatever "anti-age" beauty products we pile up in our cabinets. We buy these products knowing that they are not backed up by science, but we don't call it alchemy anymore.

On the other end, modern science is rapidly advancing, and for the first time in human history, it could open the door to real possibilities for slowing aging. As a growing number of wealthy individuals show interest in the promise of a longer life, more investments are flowing in this particular niche of scientific research. The primary purpose of these studies is to understand the biological process that causes aging on a cellular and molecular level. Acquiring the knowledge of what leads our body to grow old and deteriorate could propel the development of tools able to slow, stop, or even reverse the dreaded process.

With the advancement of this discipline, numerous questions arise. Will science succeed in quenching our human desire to defeat mortality? Is it actually desirable to reach this farfetched horizon? What social and economic repercussion could be brought about by an extended life expectancy?

I. Immortality trough history, at the crossroad of fiction, art and religion

I.I Always start with why

The race to bottle the fountain of youth is old as the human species itself. Before diving into a brief recapitulation of the search for eternal life through history, we might ask ourselves an apparently simple but inherently intricate question. *Why do humans long for eternity?*

One answer might reside in the peculiar trait that makes humankind different from any other species. Using Aristotle's words, we are "rational animals"; we look for the reasons behind phenomena to rationalize them, just for the sake of knowledge.

To understand what makes us the only rational animal on the planet, we need to go back to the moment *Homo sapiens* became the only species of hominid surviving, whereas other early-human ancestors went extinct. In fact, when *Homo sapiens* first appeared on Earth around 200.000 years ago, it wasn't the only hominid. There were at least four others: *Homo neanderhalensis* (aka Neanderthals), *Homo luzinensis, Homo floresiensis* (also known as the "hobbit" due to its tiny stature), *Homo denisovensis* and surprisingly *Homo erectus* lived amongst *Homo sapiens* for a long period of time. Then, for multiple reasons, about 50.000 years ago, we remained as the exclusive hominid existing. Different theories are trying to explain this strange phenomenon. Ian Tattersall, a New York paleoanthropologist, considers a detailed analysis of the stone tools primordial human species developed. *Homo sapiens* distinguished itself as a species when its stone tools became more decorated and intricate. This turning point is important because it suggests that humans of this species started to apply symbolism to everyday objects. Moreover, it is also around this time that cave art reaches its peak and becomes more intricate, while there is little evidence of art produced by the other hominids. However, this symbolism didn't appear as soon as *Homo sapiens* evolved; it arrived after millennia of evolution. The evolved ability to assign symbols to objects paved the way to develop spoken language, and with that, the ability to process and share information. We know that most animals have their own language and are able to communicate with each other. What sets humans apart is the ability to elaborate abstract thoughts, share them with the community, and believing in non-concrete concepts. That is the unique power of mankind: men can create stories to give meaning to and rationalize complex phenomena.

Having said that, we have our answer: humans created the concept of immortality in order to rationalize the sense of death. Defeating death is an idea that stems from the fear of dying, and it also gives more meaning to the work one has done during a lifetime. To make peace with death we need to believe that life goes on in some way.

The most widespread attempts at defeating mortality were through spiritual immortality. People believed, and some still do, that after physical death, the spirit or soul or some intangible form of one's consciousness would still be present in another realm of life, for example, reincarnation, paradise, afterlife, etc.

I.2 EARLY HISTORY

Now that we have an idea as to why humans are so fascinated with overcoming death, let's travel through history to see how people from various eras tried to solve this issue.

Thoughts of immortality go back to the *Paleolithic era*, the early phase of the Stone Age. Archaeologists found tangible proof of early hominids' hope in a postmortem life. They discovered that, tens of thousands of years ago, Neanderthals used to bury their dead in fetal poses. The fetal position is symbolically associated with birth, thus positioning corpses in such a fashion indicates hope for a posthumous rebirth.

In the *Neolithic era*, tribes from all over the world had different rites and ceremonies that manifest their belief in postmortem life. Some of them buried food with the corpses to provide them with sustenance in the crossing to the afterlife. Other Neolithic people in China and Mongolia believed that jade stone would prolong life or even confer immortality. Because of that, they used the precious stone as decoration for many ceremonial objects such as burial suits.

Those few examples described above are some of the many regarding prehistorical societies. Now let's see the quests to reach immortality at the dawn of history.

The first written piece of literature to date is the *Epic of Gilgamesh*, dating circa 2500 BC. The story of the incredible superhero-like king was conceived by one of the world's first great civilizations, the Sumerians. Sumer civilization emerged between the late Neolithic era and the early Bronze Age between the sixth and fifth millennium BC, located in Mesopotamia. Sumerians created a proto writing composed of cuneiform script and illustration engraved in clay tablets. The Epic of Gilgamesh is both the first example of written literature and the first time that the quest for immortality appeared in writing. It is indeed curious that defeating mortality was a central topic for the first survived fictional poem. Archaeologists discovered the tablets at the Nineveh library, an impressive collection of around 30.000 tablets of all the literature and documents of ancient Sumer, Babylonia, and Assyria, created by the last Assyrian king Ashurbanipal (669-631 BC). In the story, Gilgamesh is a demigod king driven by violence and war, softened in his ruling by Enkidu, his companion. In the poem, the search for immortality is prompted by Enkidu's death. When the king's friend dies, Gilgamesh suddenly becomes aware of his mortality and starts looking for a way to escape from its grasp. He is directed to an immortal man, Utnapishtim, to find the secret to eternal life, after many tests Utnapishtim sends the king to the bottom of the ocean to collect a rare plant that is supposed to make him young again. Gilgamesh retrieves the plant with great effort, but it is stolen from him before he has the chance to use it. Thus, the great king failed in his pursuit, eventually dying as foretold by his destiny.

Contemporary to the first Mesopotamian settlements was the *Ancient Egyptian civilization* (3200 BC to 300 BC). We are all familiar with the complex but fascinating religion it crafted. Hundreds of gods were involved in every aspect of everyday life and worshipped by everyone, from the modest servant to the Pharaoh himself. The crucial topic of this intricate faith was the passage from life to death. Consequently, one of the most famous scripture from this epoch is The Book of the Dead. It is a collection of spells and prayers formulated to assist the passage through the underworld into the afterlife. This manuscript, as well as the remains of this great civilization, tells us of a population obsessed with death. From colossal pyramids to the incredibly conserved mummies, Egyptians clearly believed in a continuity of life after corporeal death. According to their beliefs, life after death was an identical copy of mortal life, because of that they buried their dead with everyday objects, food, clothes, and weapons. The goal of preserving the corpses and providing them with every necessity was to ensure a safe and comfortable journey to the afterlife. But what appears to be a fixation on death is rather an obsession with life, a way to ensure continuity after the inevitable perishing of the body, a way to attain immortality.

Ancient Greece was the crib of fine art. Everything about this culture oozes with beauty. As we might already suspect, all this love for beauty inevitably leads to the search for eternal youth. In fact, the mythological story of the Fountain of Youth might have originated in Greece from the words of the historian Herodotus (484-425 BC). In one of his reports he wrote about the Macrobians, a peculiar group of people known for their longevity and youthfulness. In his writings, he speculates that the source of these people's longevity and strength could have been a pool of water in which they regularly bathed. His hypothesis probably takes inspiration from Greek mythology, where a source of water was already tied to the concept of youth. Hebe, the goddess of youth, is represented as a cupbearer on Mount Olympus. Perhaps the myth of the Fountain of Youth might have stemmed from this mythological figure. More than a century later, intrigued by Herodotus' legend, Alexander the Great (336-323 BC) is said to have searched for the Fountain. His quest is narrated in the *Romance of Alexander*, a 3rd century account of his life. However, the romance is largely fictional, adding that to the fact that Alexander died at 32 years of age, we can confidently conclude that he did not find the source of eternal youth.

So far, we have considered spiritual and theoretical approaches to immortality. However, some ancient cultures went as far as creating potions with the hope to stop aging, thus paving the way for the introduction of alchemy.

During the Qin dynasty (259-210 BC), in *Ancient China*, the earliest attempts to concoct the Elixir of Life took place. The emperor Qin Shi Huang became obsessed with finding a cure for his mortality. Not only did he send out numerous expeditions to find the Elixir of Life, but he was open to test chemical potions that would eventually lead to his death. Chinese Taoists believed that some minerals and metals, such as mercury and cinnabar (an ore of mercury), possess incredible proprieties, including strength, longevity, and eternal youth. The emperor's physicians advised him to cure his mortality by consuming some mercury pills. Those pills poisoned Qin Shi Huang to death, achieving the opposite effect instead of providing the immortality he coveted.

Lingering a little longer in the Asian territory, we find that *early Indian cultures* (400 BC-800 AD) practiced *Rasashaastra*, a branch of Ayurveda that translates as "The science of mercury". Similar to Chinese culture, ancient Indians believed that mercury was the key to longevity, and they used it accordingly. However, mercury was not the only substance used to slow aging effects; some fruit, mushrooms and fermented plant saps were other common ingredients for ayurvedic treatments.

1.3 MEDIEVAL TO MODERN TIMES

Let's proceed on our journey to the dark Middle Ages. We know from folklore and modern adaptations that this period of time rife with stories of power, treasures, and immortality, awaiting the intrepid explorer willing to find the source. From the power-figure of Prester John to the Arthurian legends; from the explorer Ponce the Leon to the Bible's nods to immortality; from the search for the Holy Grail to the Philosopher's Stone, and many other well-known adventures. Most of these recounts turned out to be fictional, nevertheless they still shaped many cultures and affected peoples' lives. Those are good enough reasons to consider them in our route throughout centuries of immortality beliefs.

The *Christian Crusades* period (12th-13th century AD) was a breeding time for incredible legends and quests. In such a dark time burdened by terrible wars fought in the name of religion, some found solace or incentive in extravagant missions. One of these pursuits appeared in 1145, sprung from a mysterious letter directed to the Byzantine Emperor by *Priester John*. The letter presented John as a catholic priest-king that ruled a Christian kingdom in an unknown location, either in the largely unexplored Orient or Africa. According to the letter, John was a powerful priest and king, descended from the Magi that paid homage to the infant Jesus. Aside from the supposed lineage of the king, another version of the letter, circulating in 1165, described his wondrous kingdom. Under his domain no people sinned; he had an immense army ready to conquer the Holy Land (Jerusalem) and other peculiarities like the presence of rivers of gold and the fountain of youth in his castle grounds. During the Crusades' time, having a potent Christian king at war with the infidels was a powerful recruitment and propaganda tool. It figured as an ally to Medieval Europe that hoped to regain Palestine from the Muslims. In the 13th and 14th centuries, many travelers went looking for the alluring tales of gold and eternal youth. These explorers are still renowned nowadays, some of them are Giovanni da Pian del Carpini, Giovanni da Montecorvino, and Marco Polo. Even though they did not find immortality or richness, they are responsible for the first contact between European and Eastern cultures. Priester John's letter remained relevant up to the 15th century, even translated into multiple languages. Only in the 1600s Europeans concluded that he was a fictional character and never really existed.

Jumping a bit forward, we arrive just in time to see Christopher Columbus' ships departing from Spain. *Juan Ponce De Leon* (1474-1521) is sailing aboard one of them, and he will become the first governor of Puerto Rico. He is notorious for being the first European to have set foot in Florida, and he even named it. During his settlement in the new world, De Leon heard of the Bimini island (now the Bahamas), where a miraculous spring could rejuvenate its drinkers. That rumor was one of the reasons he continued receiving funding from the Crown to keep exploring the continent. As with every other person that tried to find immortality or its source, De Leon did not succeed. However, we cannot say that these quests were useless; in fact, they are in part responsible for the accidental discovery of both the East and the West lands.

Going back to the Crusades' time, another monumental myth emerged, the *Holy Grail*. It first appeared in the Arthurian legends written by the poet Chretien de Troyes in 1190. Initially, it wasn't Holy at all; in fact, the Grail was probably inspired by Celtic folklore and only later combined with religious figures. Whether it was the Celtic magic cauldron that granted a never-ending life, the chalice from which Christ drank during the Last Supper, or the cup in which sweat and blood of Christ were collected during the crucifixion, the power that it bestows upon whoever drinks from it is the same: immortality and power. One could consider that a pious Christian thinking of immortality could be considered a heretic, as only the divinity he worships can be without the burden of mortality. However, in a passage of *Genesis*, from the Old Testament, immortality is within reach. The paragraph places the Tree of Life beside the Tree of Knowledge (well known for the forbidden fruit). "And the Lord God brought forth of the ground all manner of trees, fair to behold, and pleasant to eat of: the tree of life also in the midst of paradise..." (Gen. 2:9). The tree's fruit were supposed to confer immortality and incorruption to those eating it. This shows that the concept of eternal life is rooted in the foundation of ancient religions, including Christianity. Unfortunately, since Adam and Eve were thrown out of the Garden of Eden, humans won't ever have the opportunity to grab one of those delicious fruits.

Similar to the Holy Grail is the *Philosopher's Stone*, the pillar of Alchemy. As we remember from the previous chapter, ancient populations tried to defeat mortality either by conceiving complex ideas of an afterlife or by actively creating miraculous potions or elixirs. In particular, early Chinese and Indian people were the ones that laid the foundations for Alchemy with their studies on mercury. Alchemy is not so much a pseudoscience but a protoscience, considered to be the precursor of modern chemistry and medicine before the scientific method was developed. Nowadays, we are still acquainted with some of the most popular goals of this faded discipline, one of which is creating the aforementioned Philosopher's Stone. Its importance resides in the capability of turning any metal into gold and could purportedly produce the Elixir of Life that bestows eternal life. This field of study thrived particularly under the Islamic influence and only later became popular in Europe during Medieval times. No alchemist succeeded in producing this miraculous stone, but alchemy has been extremely useful for paving the way for modern scientific disciplines and medicine.

In the *17th century*, Alchemy changed the name in *Chymistry* and represented the slow transition from Alchemy to Chemistry. The greatest minds during Enlightenment Era were involved in these studies. Even Isaac Newton was one of these chymists. On several handwritten pages of his laboratory notebooks, he sketched alchemical symbols and formulas, right next to pages filled with explanations of optical and physical phenomena. In these manuscripts, he also writes about *sophick mercury*, an abbreviation for philosophical mercury, a synonym for the Elixir of Life. Even for Newton, the line between mystical alchemy and physics is not well defined. This quirky discovery raises many questions, was the founder of classical physics an alchemist? Was he pursuing science because fascinated with the mystical possibilities of the Philosopher's Stone? Once again, we have to thank the quest for immortality, this time for Newton's scientific discoveries.

2. THE SCIENTIFIC POINT OF VIEW

The race to bottle the fountain of youth does not end with Newton and his fellow alchemist/scientist of the Enlightenment Era. Immortality and eternal youth remained a relevant topic, mainly in literature and philosophy. From Kant's Postulate of Immortality to Freud's hypothesis as to why we relinquish the idea of dying, this notion still tickles the human mind.

Besides philosophical and psychological theories, we are accustomed to seeing the topic of mortality and its opposite virtually everywhere. Literature shows plenty of interpretations of this intricate and fascinating theme. Oscar Wilde's Dorian Gray and Bram Stoker's Dracula are perfect examples of a disillusioned society that sees dodging death as an immoral dejection.

The obsession with long life and youthful and healthy appearance is still a powerful drive in our society. Many still find solace through the promise of salvation and soul immortality that religion offers. But more and more people are looking for quicker and earthly solutions. The first idea that comes to our mind when we think about looking young indefinitely is plastic surgery. It is the prime example of a quick, but costly, way to avoid the tell-tale signs of passing time. However, surgery is invasive and very expensive, thus not available to whoever wants to look younger. That is why the cosmetic industry is increasingly thriving since the 20th century, especially during the roaring '20s. The global market value of this sector is a whopping 500 billion dollars as of 2021 and estimated to reach 800 billion by 2025. A large piece of this business is the anti-aging market, also increasing steadily during the decades. Taking advantage of this profitable trend, many companies develop and endorse a plethora of anti-aging products that supposedly keep people from growing old. Unfortunately, there is little scientific evidence confirming that these pills, lotions, food supplements, etc., can stop or reverse the aging process. The great majority of these products only address the aesthetic consequences of age rather than the process itself. The industry's great value and the ever-growing interest in contrasting aging is a double-edged sword. On one side, it attracts snake-oil salesmen and charlatans to trick customers into buying ineffective products claiming to extend lifespan. On the contrary, having wealthy people pouring money into this field of research could create concrete possibilities.

In any case, aging is not good for us but is surely a good business.

2.1 LONGER EXPIRATION DATE

Century after century, alchemists evolved into chemists, the fountain of youth into medicines, immortality into longevity. Our expiration date evolved too. It is evident when observing the rising trend of life expectancy, especially in the last few centuries. From the appearance of *Homo sapiens* up to the 19th century, the average lifespan fluctuated between 25 and 40 years. During the 1800s, basic notions of hygiene and public health caused a dramatic increase in longevity, bound to rise again during the 20th century. Today the average life expectancy is the longest ever reached, around 80 years, depending on regional and economic differences. There are also some lucky communities where people live longer than average. They are the five Blue Zones: Okinawa in Japan; Sardinia in Italy; Nicoya in Costa Rica; Ikaria in Greece and Loma Linda in California. The most famous are some towns in Sardinia and Japan. These areas are a popular topic for longevity research. Many diets and lifestyle examples are designed using these zones as a reference and adopted by people trying to reach at least a centenarian age. Besides these isolated cases, will global life expectancy continue to increase as the trend suggests? Some experts believe that we are reaching a plateau, whilst others don't exclude the possibility of a steady rise in our lifespan as medicine and technology progress.

2.2 TWISTS OF NATURE

A smart way to try and understand how to solve the aging riddle is to look at nature. Billions of years of evolution can create peculiar processes in some species that are often used to solve human problems. Could we apply this notion to aging? Let's have a look at the best cases in our biosphere. Nature offers a wide range of lifespans. On one side of the spectrum, there is the insect *Ephemeroptera*, also known as Mayfly, that only lives an adult life of thirty minutes. On the other side there is the Greenland shark, *Somniosus microcephalus*, the most longevous vertebrate existing on the planet. Its lifespan is estimated to be between 300 and 500 years. But outside this spectrum, there are a few species that escape nature's aging mechanism. One of these "glitch in the system" specimens is the lobster, and it is perfectly fitting in our quest for immortality. Lobsters don't get old in the way we are used to considering. We often associate growing old with a general decay of our organism: we become less active, less fertile, less energetic, we lose the tonic appearance of youth. Lobsters don't suffer this destiny; instead, they keep growing, becoming increasingly big, strong, and fertile. Hence are they immortal? No, they die, not from the aging process, but from exhaustion. In fact, this animal is an invertebrate, and to protect and sustain itself it needs a shell. The older the animal, the bigger its body is, and the bigger the shell needs to become. Eventually, the shell becomes so big that the energetic cost to produce it and sustain it exceeds the animal's strength, thus it dies from exhaustion during the last molting. All of this means that lobsters could stay alive indefinitely, taking the heavy shell out of the equation. Researchers are investigating the scientific processes that allow this animal to remain healthy for such a long time. Have we finally found the first clues leading towards the real fountain of youth? Even weirder than the lobster is the immortal jellyfish, *Turritopsis dohrnii*. This species can escape aging forever. Instead of aging, in fact, it becomes younger. Discovered in 1998 and studied ever since, these jellyfish can reverse from the adult stage (medusa) to the immature stage (polyp), and from there growing into maturity again. This strange, back and forth, life cycle can continue forever, or up until the organism succumb to predation, accident or disease. One last example of an extraordinary organism is the tardigrade, also known as water bear, has a pretty short lifespan. However, when put in stress conditions, it's able to survive thousands of years, perhaps even forever. That is possible by entering a special metabolic state: cryptobiosis. In this state the animal is completely dehydrated and every molecule in the cell stops exactly how it is, without being damaged. At any point, if conditions become favorable again, the tardigrade can revert to its active form. It's an incredible example of a complex animal being able to press pause and play on life.

2.3 WHAT IS AGING?

So how do we get from observing prodigious species to finding a "cure" for human aging? To answer the many interrogatives posed in this dissertation, we have to start with the most fundamental. What is aging? Scientists have managed to find definitions of death, life, lifespan, even immortality. However, there is no consensus around aging, mostly descriptive definitions. Everyone can differentiate between a young and an old person, but it has been proven difficult to give a precise definition of the biological process that causes aging. A popular attempt at explaining this phenomenon is that aging is the gradual loss of biological integrity, a scientific way to say that as one gets older, things start falling apart. Our senses are not as sharp, skin gets wrinkly, hair thins out and becomes grey, organs get slowly faulty, bones became fragile and break more easily, arteries harden, memories fade. According to WHO aging results from the consequences of the accumulation of cellular damage overtime, leading to a decrease in physical and mental capacity. A great portion of cellular damage involves DNA. DNA is the molecule of life, every living organism has one. It is the instruction manual inside every cell, it defines what we are, how we appear, how we behave. It is a personal barcode, unique for each one. Without DNA, or with a highly damaged one, a cell cannot live. Considering its importance DNA must be a very stable and well protected molecule. And it definitely is. However, the longer we live, the more we expose our body, therefore our cells, therefore our DNA, to potential damage. When our DNA gets damaged it gives the cell the wrong instructions, thus creating an aberrant cell that could cause problems for the organism. These aberrant situations are kept in check by many repair systems that promptly correct the damage in our instruction code. When the DNA damage is too severe for an adequate correction, or when the corrective pathways are not working correctly, the faulty cells need to be eliminated. To prevent reaching this out-of-control state, there are the telomeres, some sort of chromosomal clocks that limit the number of times a cell can divide. Thus, aging is literally encoded in our DNA, a natural limit of biology, seemingly unavoidable. When a cell arrives at the end of its predetermined life, controlled by telomeres' length, it doesn't die but enters a senescent state. This means that the cell cannot divide and proliferate anymore, but it is not able to function correctly anymore. So, by just sitting there, it causes inflammation and irritation in the surrounding tissue. As we grow old, the number of senescent cells increases, causing long-term inflammation in many tissues. This typology of inflammation is believed to be at the basis of many age-related diseases as Alzheimer's disease and arthritis.

Why don't we just prevent telomeres from getting shorter? That would create immortal cells, able to proliferate endlessly. Unfortunately, this is not the key to immortality. In fact, we have identified cells that can replicate uncontrollably: cancer cells. At the end of the day telomeres are a mechanism evolved for a precise goal, they keep cells healthy and avoid the development of crazy and disruptive cells. It might not be a good idea to mess with this system.

2.4. ETERNAL SHIVERS

"A fulfilling life doesn't have to end. When today's medicine gives up, cryonics takes over".

What seems the first line of a science fiction novel, is instead the headline of a real company. How about cheating death by indefinitely preserving our body until future medical progress is able to revive it? It's not a futuristic movie, it is an option that three companies around the world offer. They claim that maintaining the body at subfreezing temperatures could stop its deterioration, allowing to pause the dying process. This technique is called cryopreservation. The teams that offer this service follow a precise pipeline. Cryopreservation can begin only after the patient is declared legally dead. Legal death is when the individual has sustained irreversible cessation of circulatory and respiratory functions. Simply put, one is legally dead when the heart and lungs stop working autonomously. When that happens, many other cells of the body and even some tissues are still functional, for a short period of time. That's when the cryopreserving team comes into play. As soon as the client is declared legally dead, the body is put in an ice bath to slow the chemical and biological reactions that occur after death which lead the body to deteriorate. The following step is vitrification, not freezing. Freezing is a highly damaging process for biological matter. That is because cells are made up of a large percentage of water, when water freezes it creates crystals that pierce through the membrane of cells, popping them like balloons. Instead, vitrification is a far gentler and efficient process. It involves the complete substitution of water with a fluid called cryoprotectant, a substance similar to anti-freeze, that doesn't form crystals at very low temperatures. Through this slow process the complex biological structures that form the human body (tissues, organs, blood vessels, etc.,) supposedly stay intact, like frozen in time. When vitrification is complete, the body is conserved in liquid nitrogen (-196°C). Advocates of cryonics hypothesize that in this state the central nervous system is in a suspended state that reminds us of the tardigrade's cryptobiosis. The companies that provide this service offer the prospect, without any assurance, that one day in the future medical science and technology will be able to defrost these conserved bodies and relive them. It all sounds exciting, and a bit scary, but let's consider how scientifically plausible this process is. Cryopreservation is a common process used in modern science to efficiently store living cells, such as blood cells, bone marrow, sperm and embryos. Moreover, it has been observed that brain structures involved in personality and long-term memory maintain their structure for some time after clinical death. Finally, there have been successful experiments demonstrating that some of these cerebral structures are preserved with cryogenic treatment. However, the likelihood of success for conserving entire bodies is very low. Researchers are still failing to cryopreserve organs for easing transplants procedures, if we are not able to perfect this process on a single organ it looks very unlikely to succeed with a whole organism. Ultimately, trusting this process is an expensive leap of faith, not in religion but in science. If one has the means to cover the cost of this procedure, there is an extremely little chance of being relieved. Still, for how little of a chance, is still higher than coming back to life after cremation or burial. Nowadays almost 300 people are actively cryopreserved in facilities, while thousands are already on the waiting list. If you are looking for reviews, it's not your lucky day, no living person has been defrosted yet.

2.5 WHEN NATURE DOES NOT PROVIDE

During the last few years, the scientific world has been shaken up by incredible breakthroughs. Biotechnology has transformed most science fields. Research has greatly improved thanks to recombinant DNA technology, genome editing tools like CRISPR, big data, and artificial intelligence. We have entered the 21st century by sequencing the first human genome, and in less than 20 years from a proof of concept it has become a standard practice from clinical diagnostics to the discovery of our genealogy. In our journey through millennia of *Homo sapiens*' history, we noticed a consistent trend: humans trying to find a way to escape mortality and always failing. Instead of providing us with a compass pointing towards the Fountain of Youth, biotechnology might offer us the means to encode immortality within ourselves, writing it in our genomes.

The exponential expansion of new possibilities in science has attracted the most optimistic anti-aging researchers. Amongst them one stands out, Aubrey De Grey, a British biogerontologist at the University of Cambridge. Biogerontology is the study of the biological processes that causes aging and age-related diseases. In 2005 De Grey, an optimist in his research, founded SENS (Strategies for Engineered Negligible Senescence) Research Foundation. The non-profit Californian organization «works to develop, promote and ensure widespread access to regenerative medicine solutions to the disabilities and diseases of aging». The incredible goal of the foundation is to achieve Negligible Senescence. It sounds like a complex concept, let's break it down in simpler terms. Senescence is the gradual deterioration of functionality and integrity of an organism as aging progresses. With the passing of time, organisms show an increase of death rate and a decrease in fecundity. Negligible means "not detectable". The two words coupled with each other indicate the final scope: obtaining an organism that does not become old in a detrimental way. It would change the paradigm by decoupling aging with an idea of infirmity. We have already encountered such cases in lobsters and jellyfish. De Grey's team employs multiple strategies to reach its target: stem cells and tissue engineering, design of novel enzymes, mitochondrial restoration, immunotherapy to eliminate senescent cells in the organism, and many more. However desirable this aim is, the majority of the scientific community is skeptical. Even though some of the strategies are supported by reliable scientific literature, many critics argue that the biological processes that govern aging are far too complex and still not understood for SENS to be viable in the immediate future. Many consider De Grey's research goals outlandish, an accusation most visionaries must accept. Some remain in the realm of science fiction, some don't. In 1900 anyone predicting a life expectancy near the hundreds would have been considered crazy, less than a century later most of us can expect to live to the eighties or even over the nineties. Who knows if in the future decades De Grey's vision will become a real medical possibility.

2.6 OF MICE AND MEN

On the same track is synthetic biologist pioneer George Church. The Professor of Genetics at Harvard Medical School and founding member of the Wyss Institute for Biologically Inspired Engineering, is paving the way for immortality in a more subtle and scientifically accurate way. Aging reversal has been proven effectively in about eight different animals, such as flies and worms. The treatments studied cause faster reaction times, cognitive improvement or repair of damaged tissues. However, it still isn't available for humans. It is for some lucky mice though. Dr. Church led some studies on model mice based on gene therapy. By adding some specific genes, the defective animals restored regular heart and kidney function and balanced levels of blood sugars. With the rising of GMO, the general public showed reluctant towards genetic engineering. Because of that scientists, including Church, are focusing more on regulating the expression of a gene. Instead of modifying the genome in a way that is hereditable for its offspring, it only increases or decreases the amount of product it encodes. This way is much safer, less tricky to market and doesn't change permanently the genome in a hereditable way. The biologist's end goal is to create an "anti-aging vaccine", by injecting a few shots of his gene therapy cocktail the patient will stop or reverse the process altogether. His idea stems from the fact that as people age genes that promote healthy, vigorous and overall youthful functions turn off. By switching these genes back on, it would be like turning back our biological clock, thus reversing the aging process. The laboratory tested many genes considered to be implicated in longevity, both one at a time and in different combinations. Eventually they found three that worked the best: FGF21, sTGFR2, and Klotho. The team constructed the gene therapy vectors using an adeno-associated virus AAV8 that contains the genes needed. These constructs were then injected in mouse models of various diseases (type II diabetes, heart failure, and renal failure). The results were eye popping, proving that co-administration of FGF21 and sTGFR2 could treat all the conditions, thus improving health and prolonging survival. The following step is translating the results in dogs. In 2019 Church and collaborators launched a new company that plans to use gene therapy to restore youth and extend the lifespan of Cavalier King Charles Spaniel dogs. The technology is applied to stop or reverse mitral valve disease, a deadly condition that affects most Cavalier King Charles spaniels and leads to heart failure. TGF, one of the promising longevity genes successful in mice, is involved in the process that leads to scarring and thickening of the mitral valves, thus electing it as candidate for this clinical trial on dogs. Why choosing dogs after mice? Not only dogs are good model for humans, but they need less time to prove if a therapy is increasing longevity, thus generating data for FDA approval more quickly. Moreover, dogs and their medical treatments are big market areas. Having a marketable product could pay for the research and development of the human therapy, while the collected data provide solid background for efficiency and safety. In the next few years, we'll see the results of the dog's clinical trials. If all succeeds, human trials are next on schedule. For humans the process is much longer, so the first topics on Church's agenda are to treat as many age-related diseases, including cancer and neurodegenerative disease, after the already tested osteoarthritis, high-fat obesity, diabetes, heart damage, and kidney disease. According to Church their gene therapy cocktail should impact all, or most, diseases at the same time. That is because it is basically convincing the cells that they are younger, with all their repair mechanisms fully operating. Right now, the technical challenge is the delivery of the genes inside the organism, they need a shuttle that carries them exactly where they need to go.

2.7 OLD PEOPLE, YOUNG BUSINESS

As a consequence of the increase in life expectancy, we are witnessing a global greying. The world population of over-60s has more than doubled since 1950 to almost a billion and is expected to double to two billion by 2050. A growing proportion of the population is made up of old people. That has heavy consequences on the public health system. Unfortunately, as of now, older people are more likely to suffer from chronic illnesses that put more pressure on the social system. These projections are not just numbers sitting inside dusty UN reports, many countries are actively trying to improve on the issue. For example, in 2019 the UK set up a challenge of adding five more years of healthy life to all its residents by 2035, thus prolonging the healthspan. This shows that governments are actively interested in boosting medical research to relieve the public health system. Scientists and doctors are now considering whether the key to curing age-related conditions is to target aging itself. Because of this ever-growing interest, spanning from private investments to public ones, many companies focusing on anti-aging therapies are sprouting on the market. Let's visit some of the most promising visions. Biotechnology company Telocyte focuses on experimental drugs for treating Alzheimer's at the cellular level. They center their research on the underlining cause for the development of the disease, you guessed it, aging. Telocyte is aiming to reset cell senescence, a topic we have already encountered. To achieve that, the company is focusing on telomeres, the genetic clocks that dictate the lifespan of a cellbased on the number of replications it went through. Telocyte does not want to be labeled as an anti-aging company; however, its president recognized that it is a contradiction because «the only way we can treat Alzheimer's is to reverse aging at a genetic level». If the common cause at the basis of age-related diseases is cellular aging, the line between medicine and life extension is bound to be increasingly blurry. The Californian company Unity has a more straightforward scope: developing pharmaceutics to slow, halt or reverse aging. Their strategy implements senolytics, molecules that clear the organism of senescent cells. The startup has proved the efficiency of the drug on mice. A typical model mouse lives two years and its aging process externally manifests in a similar fashion compared to the human one: thinning hairs, turning progressively blind, joints become arthritic, less energetic, and more sedentary. However, mice treated with the experimental drug designed by Unity labs are still good-looking, active, healthy, and overall still youthful at two years of age. The company's success has attracted interest and Unity was recently valued at a whopping $700 million by investors. Telocyte and Unity are only the tip of the iceberg in this fruitful research field. More and more investors are being attracted to the game. A prominent hotspot is the Silicon Valley, where longevity is amongst the most pressing of our time, alongside climate change and clean meat. At the forefront of the Valley, Google has poured billion dollars founding in its Calico (California Life Company) which goal is to discover and develop technologies that will allow people to live longer and healthier lives. At the same time, big names as Amazon's Jeff Bezos and PayPal's Peter Thiel are funding companies investigating gene therapy and anti-aging drug discovery, including the already discussed Unity Biotechnology. We might not become immortal in the short-term future, but science is quickly catching up with the long-matured aspirations.

2.8 WITH BIG INVESTMENTS COMES BIG RESPONSIBILITIES

The hype surrounding this new industry attracts many snake-oil salesmen, ready to take advantage and earn easy money on the desire to defy death. A fitting example of a scam company is Ambrosia, right in the middle of Silicon Valley. The company offered infusions of young people's blood as an anti-age treatment to its clients looking for a quick shot at eternal youth. In 2019 an FDA investigation shut down the business because the so-called medication was neither tested nor approved by any institution. Regardless, it reopened after a couple of months with a different name. BioViva CEO Liz Parrish claims to be patient zero in her own experiment, the goal: stop biological aging. The experiment is supposedly an untested gene therapy to extend the telomeres of her cells and a different one to restore muscle tissue. According to her, she stopped the biological clocks making her younger than she is. In interviews, she promises that in the next few months the treatment will be available for the market. However, Parrish studies are not verified or approved by any framework. And digging deeper in the actual project of the company, it is not an actual vaccine against aging, but a telomerase therapy for Alzheimer's disease patients in Mexico, away from the FDA jurisdiction. Many researchers and bioethicists, playing by the rules, worry that longevity startups taking shortcuts to maximize profit will slip into a "Gelsinger moment". The unfortunate case of Jesse Gelsinger who died in a mismanaged gene therapy trial in 1999 and caused a temporal banishment of all gene trials in the US. Making a similar misstep would cause another setback of all gene therapy research. According to market previsions, these deceiving startups, are unlikely to bring any real product on the market. They thrive from the conspicuous investments they lure in by making gilded promises. But underneath the golden surface, embellished with scientific definitions and complicated words, is just an empty well and no spring of eternal youth. To protect the eager and inexperienced consumer from scammers, regulation frameworks, governments and peer review have to keep a very tight leash on companies and laboratories claiming to have found a way to bottle the fountain of youth in a syringe.

2.9 THE NEAREST HORIZONS

At this point, we have seen a lot of advancement in the longevity research area. Some of it looks definitely promising, bringing us closer to an era in which we might live and be healthy for a long time. Some other concepts look like they are straight out of a sci-fi novel, almost too avantgarde to be actually feasible. All things considered, it seems that, for the first time in millennia, we might be on the right track to unveil the secrets of longevity, if not immortality. We could be in the right direction, however the road is still very long. Not because of lacking interest, but for a more formal reason. Government agencies and medical regulators don't consider aging as a treatable condition. Thus, it is extremely difficult to have a treatment approved when its main goal is to slow the aging process or taking us closer to a life without the restraint mortality imposes. If a company or research laboratory wants to develop and market a product with anti-aging effects, as of now, it has to present the drug as a medication for some recognized illness, for example osteoarthritis, muscle loss, Alzheimer's. This trick has already been put to use as many are looking at already approved drugs and active molecules to see if they have interesting effects on longevity. An example of this process is metformin. The molecule is already in use for its therapeutic effects against diabetes. In fact, metformin is the most prescribed therapy for type 2 diabetes. It allows patients to improve their blood sugar levels by controlling insulin sensitivity. Some studies also showed that the compound can slow cancer progression, inflammation and age-related pathologies. Its positive effects on lifespan are already confirmed on worms, flies, mice and rats and its safety is not a concern because it is already approved for treatment. All the prerequisite to turn metformin into an anti-aging pill are there. The major issue for having a drug approved for its aging effects on human beings is time. It would take too long to prove that a therapy can effectively slow aging. So, for a company to support itself for that many years, it needs to market a product faster, thus labeling it as a treatment for an age-related disease. The company Unity Biotechnology created a product able to keep mice young and healthy even after two years of age, the therapy is being labeled as a cure for arthritis to obtain approval from FDA. Its effects however will not be confined to that condition, in fact, according to Unity's CEO "everyone will want this drug".

3. IS IT EVEN DESIRABLE?

Whenever considering anything coming out from a lab, our instinct goes to potential side effects. This ideal anti-aging therapy is not immune to that. Instead, it is a very discussed topic. By increasing lifespan, scientists are tinkering with basic biological processes evolved to optimize our life through millennia of evolution. The shortening of telomeres and senescent cells are not biological mistakes, they are fundamental to protect our organism's well-being. They keep highly mutated cells from causing broader disruption in the tissues. A cell line that naturally expresses a protein that stops telomeres from shortening (telomerase), thus allowing immortality of the cell line, is cancer. One of the defining characteristics of cancer cells is their ability to proliferate without restraints. Similarly, senescence is a mechanism that prevents damaged cells to live on, as they could eventually become cancerous. These processes were developed to protect us, so changing or deleting them might not be a great idea. Undesirable side effects aside, when the opportunity seems to draw closer on us, we might also wonder if, after all, we would really want to become immortal. As with most technological revolutions, like nuclear power and artificial intelligence, we might not be able to foresee the implications, whether they are positive or not. Also, having a society with an increasingly high number of elderly citizens would have an impact on its economy. One of the issues would be the ratio of the retired population versus the working population. This trend is already on the rise since the demographic boom that followed World War II in developed countries. There are more elderly and fewer young people replenish the workforce. If the trend is to become even more drastic, there would be enormous pressure on social infrastructures. Societies would have to redesign the way pension programs, the average retirement age, and public health are organized. Moreover, there is also the justice issue. While spiritual immortality is free for everyone to obtain through any chosen faith, becoming immortal through science would not come for cheap. Because of that, by marketing the possibility of becoming eternal, only extremely wealthy people could take advantage and benefit from it, therefore causing an incredible social, economic and ethical disparity. Of course, as with any innovation as unimaginable as the search for eternal youth is, we have to relish the many positive consequences but also critically consider the negative ones. And if we are to finally obtain the much-desired possibility of becoming immortal, would we get tired of life? Would we then long for death instead? As soon as we come closer to the realization of something we have wanted for a long time, our mind starts to ponder the real consequences. In fact, for as long as we've longed for eternity, we have always questioned its desirability.

4. CONCLUSION

Tree models to "stop" aging. Which one will come true?

It's time to hop off the train that led us to humans' quest to find a way to cheat death. We have not arrived at the last stop yet, but perhaps we are closer than we've ever been. We have started our journey with the faint hopes of reborn in the Neolithic Era, we have read the great Gilgamesh efforts. We also marveled at the Egyptian fascinating underworld, and we smiled at China and India's first naïve attempts at fabricating elixirs of eternal youth. Then, we saw some famous names and even more famous objects from the Middle Ages legends to Newton's science. Eventually, we lingered on contemporary times, our last stop of the expedition. Here we considered many different points of view and the many ways modern scientists are addressing the immortality issue and the ethical problems that could emerge from their hypothetical success. To tie things up let's see what scenarios, scientists, and demographers predict for longevity research in the future. The most pessimistic picture predicts that by prolonging our lifespan we won't obtain eternal youth, au contraire quite the opposite: prolonged senescence. Meaning that science and technology would keep old bodies living for a longer time, without any increase in quality of life. A less dystopic, but conservative view is to achieve compressed morbidity. That means that the overall lifespan would not increase, but thanks to medicine and science the plethora of chronic age-related diseases would be delayed to the final few years of life. This way, people would have a healthy life for a longer period of time within the current lifespan. Moving to the optimistic side we have decelerated aging. Its final result would be to increase the maximum lifespan. People would continue to age, but slower and over a longer time. At the extremes of the spectrum is arrested aging. By regeneration of tissue, negative senescence, improved repair mechanisms, and other technologies, we would be able to keep the aging process at bay. This way humans would theoretically be immortal. Which one will come true? I guess we can only hope to be here long enough to find out ourselves. As for now, the best shot at becoming eternal is by creating something so revolutionary that people won't forget about it for a long time, exactly what Woody Allen has done with its movies. When it comes to believing in physical immortality is still a leap of faith, not in religion but in science.

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