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CRYONICS

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Editorial Board Ralph Merkle, Ph.D. Max More, Ph.D. R. Michael Perry, Ph.D.

Editor Aschwin de Wolf

Contributing Writers Linda Chamberlain Max Marty Max More, Ph.D. R. Michael Perry, Ph.D. Reason

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Letters to the Editor welcome: aschwin@alcor.org

> Advertising inquiries: 480.905.1906 x113 advertise@alcor.org ISSN: 1054-4305

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Alcor's recent high caseload requires us to pick and choose which case reports to publish in the magazine. It's the first case report that includes a calculation of a patient's S-MIX to estimate the total time of ischemic exposure.

13 Our Recent Heavy Caseload: How Often Can We Expect This?

In the four months from early May through early September of this year (2022), we had *nine human cases* (and several pets too, but here we focus on the human only). It was, needless to say, a busy time for us with all the cryoprotections, transports, cooldowns, and the expected barrage of associated operations. It raises the question of how often we can expect happenings like this. Mike Perry revisits his earlier writings on this topic.

17 Peak Stuff: The Dematerialization of the Economy

"As the economy grows, we use a growing amount of resources." If asked whether that statement is true probably the vast majority of people would say that it is. You may find it intuitively obvious. Economic growth = more stuff = more resources. In fact, economic growth can be decoupled from growth in the amount of "stuff" we produce. In part 4 of his Getting Better series, Max More explores this little-known aspect of trends in growth and resources.

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Reports from the front line in the fight against aging.

45 Revival Update

Mike Perry surveys the news and research to report on new developments that bring us closer to the revival of cryonics patients.

Case Report A-3434

By Linda Chamberlain

Summary

Information was derived from multiple sources and was all converted to Mountain Standard Time (MST). For deidentification, dates are not shown. T-0 represents the date of pronouncement of legal death, T-X represents occurrences before T-0, and T+X represents occurrences following T-0.

A-3434 was a 90-year-old member with neuro cryopreservation arrangements who had kidney problems and a metastasized malignant neoplasm of the bladder. The member was pronounced legally deceased in California at 02:08 hrs on T-0 days in February 2022. The cause of death per the death certificate was respiratory arrest subsequent to cardiac arrest, with an underlying cause of malignant neoplasm of the bladder.

After stabilization and Field Cryoprotection (FCP), the patient was air transported to Alcor for cryogenic cooldown. The patient arrived at Alcor on T+1 days at 20:35 hrs. The cryogenic cooldown was initiated on T+1 days at 21:36 hrs and terminated on T+4 days at 20:42 hrs. CT scans were made of the patient's brain on T+52 days; the patient was then transferred to long-term maintenance at liquid nitrogen temperature.

Patient Assessment and Pre-Deployment

<u>T-99 days</u>

This was a new member with terminal bladder cancer that had metastasized to multiple organs and was going through a second round of chemotherapy. The member's height was 6'1" and weight was estimated to be 73 kg to 77 kg. Hospice care was not available because the member was still receiving medical treatment. As the member was on the Alcor Watch List, Alcor's Medical Response Director (MRD) called for a weekly update and learned that the member was in the hospital for a serious infection in the lower quadrants. Physicians also found a nondescript problem with the kidneys. There was no indication that the member would decline acutely. Alcor's MRD continued weekly calls with the member with no significant health changes.

T-36 days

The member successfully had kidney stents placed bilaterally, had been receiving frequent blood transfusions, and was experiencing increasing weakness.

T-29 days

The member was taken by ambulance to a hospital due to a fall at home. The member needed a blood transfusion, but critical shortages of blood due to the COVID-19 pandemic prevented this from happening. Additionally, the abdomen was distended.

The member had a hemoglobin count of 5.5 and had received 2 units of blood. A third unit was to be given the next day. A CT scan of the abdomen showed an impacted bowel. A discussion was held with the member about the potential for a delayed pronouncement of legal death while in in-home hospice care. The MRD and Alcor's surgeon consulted and agreed that, based on current information, a deployment was not yet justified.

T-24 days

The member received a blood transfusion, but his hemoglobin count continued to fall, there was some bleeding (location not known) and an unspecified infection (the COVID protocols made it difficult to get information, even family visits were limited). The physicians had requested a meeting with the member and the family for a palliative care discussion.

<u>T-19 days</u>

The member was discharged from the hospital. Despite repeated conversations regarding hospice, the member still had not contacted any hospice facilities. At 13:56 hrs the member called Alcor's MRD to report feeling weak and was enroute to the hospital to receive another transfusion. The member had a temperature of 39°C and at-home COVID tests showed that both the member and spouse were positive for COVID-19. The hospital had been clear that care options were limited, and the member needed to seriously consider hospice.

Suspended Animation, one of Alcor's strategic partners for standby, stabilization and transport (SST) was located near the member and a paramedic from a second strategic partner, International Cryomedicine Experts (ICE) was also in the area, so there would be immediate assistance in case of emergent need.

T-6 days

The member was now enrolled in in-home hospice care and receiving a home visit every three days or as needed depending on the member's condition. Hospice personnel agreed to inform Alcor of any changes, and as the member declined, they would schedule visits more often.

Preparation and Deployment

T-2 days

As the member had experienced a noteworthy decline over the last two days, the member's family called Alcor while the hospice nurse was at the home. The member was significantly less alert, in constant pain, and could no longer swallow pills. Regarding nutrition, the member had eaten two spoons of egg whites the day before and had half of an Ensure drink, but nothing this day outside of sips of water. The member was on Norco and sublingual morphine for pain.

There was almost no urine output. The vital signs taken by the hospice nurse were stable with a blood pressure (BP) of 128/78, heart rate (HR) of 105/min, and a capillary oxygen saturation (SpO₂) of 92% on room air.

Because this case was going to be a field cryoprotection, ICE was officially deployed for SST at 15:13 hrs. The ICE team was in the area and arrived at the member's home at 17:11 hrs. The member was alert and talking, but not oriented.

Standby and Stabilization

<u>T-1 days</u>

The hospice nurse called Alcor at 17:19 hrs and reported that the member had excessive secretions but the ability to swallow was limited. There had been little consumption of food or liquids all day. The member had received 10 mg of sublingual morphine twice that day. The nurse confirmed that during daytime hours she would be called to pronounce legal death. The after-hours line would be called for declaration after 17:00 hrs.

At 21:45 hrs the member had increased difficulty with breathing. The member's vital signs at 23:03 hrs were SpO_2 of 67%, HR 124/ min, and 30 labored respirations per minute.

T-0 days

ICE was called by the member's family at 01:43 hrs to report that the member may have gone into cardiac arrest; this time is used in this report for the time of estimated cardiac arrest.

The death certificate shows the time of death as 01:08 hrs (PST). For this report, the time on the death certificate will be used as the time of pronouncement of legal death and converted to MST (02:08 hrs). ICE arrived at the patient's home and did not initiate stabilization procedures until the arrival of the hospice nurse and the legal declaration of death (see the Discussion section).

To initiate cooling, at 02:20 hrs manual cardiopulmonary support was started while the ROSC-U device was set up and initiated. The patient was placed into a portable ice bath (PIB) made from a body bag and 120 lbs. of ice were placed around the patient (see Discussion section). The first intraosseous device (B.I.G., Bone Injection Gun) was placed in the tibial tuberosity of the right leg at 02:20 hrs to access the vasculature for administration of the stabilization medications which were initiated at 02:22 hrs (see the below Table of Medications Administered for the names of the medications). A second intraosseous device was placed in the tibial tuberosity of the left leg at 02:34 hrs to allow the medications to be delivered more quickly. A King airway was inserted; however, the balloon cuff malfunctioned and had to be removed. Without the cuff inflated, air would be free to enter the stomach and fluids could enter the airway. Therefore, no airway was used, and cardiopulmonary support proceeded without ventilation.

Cardiopulmonary support was terminated at 04:00 hrs. The HOBO datalogger did not function. As the kit had two dataloggers, the second device was used and functioned properly (see the Discussion section). After stabilization, the patient departed the residence at 04:17 hrs and arrived at the funeral home for Field Cryoprotection (FCP) at 04:54 hrs. Cooling and chest compressions continued while waiting for the transport company to arrive.

Field Surgery and Cryoprotectant Perfusion

Field surgery was initiated at 05:14 hrs. The right carotid artery was cannulated at 05:28 hrs and the left carotid artery was cannulated at 05:41 hrs. Both burr holes were completed at 05:43 hrs and cephalic isolation was initiated at 05:48 hrs and completed at 05:52 hrs. The cephalon weighed 4.7 kg, prior to cryoprotection. Fluid return was noted from the vertebral arteries, suggesting that the Circle of Willis was intact.

Bladder #1 containing B1 solution without cryoprotectant was used at 06:00 hrs to prime the tubing circuit. All refractive index (RI) readings were taken from the seepage emanating from the jugular veins. The refractive index readings were inconsistent. This resulted in only recording a refractive index reading once, at the start of the 1-hour countdown to termination of cryoprotectant perfusion (see the Discussion section).

Pressure gauges are not currently in the kit as pressure is estimated by the height of the bladders on the pole (see the Discussion section). The teeter-totter device that allows a smooth mixing of different solutions of perfusate was found to be broken, so bladders were hung one at a time (see the Discussion section for a more detailed explanation).

The gravity-induced perfusion flow was initiated at 06:16 hrs with Bladder #2 containing nM22 cryoprotectant with a concentration of 0.05 CNV. See the below Table of Concentrations (Brix) of nM22 solution for the precalculated refractive index of the individual bladders, and the refractive index of the effluent samples.

The refractive index of the effluent was 50.3 Brix at 09:05 hrs (see the Discussion section); the 1-hour countdown to termination of cryoprotectant perfusion was started.

Per the cryoprotection protocol, the ramp is to be paused at 30 Brix (50% of the desired terminal concentration) to allow the patient to come to osmotic equilibrium. When the bladder system is used, bladders 6 & 7 represent the pause. The cephalic enclosure and the chiller are switched from $+3^{\circ}$ C to -3° C operation. At the end of the 30-minute pause, the ramp is resumed at the maximum addition rate (maximum without losing total volume in the circuit) to go to 105% of the desired end concentration (52.5 Brix) and held between 102% and 105% concentration until the terminal concentration is obtained.

Field cryoprotection ended at 10:08 hrs. The refractive index was 50.3 Brix. Perfusion was terminated at 10:10 hrs. The cephalon weighed 4.9 kg at 10:15 hrs, after cryoprotection. This was a weight gain of 0.2 kg, or 4 percent.

Patient Transport

The patient was placed in a neuro shipping container and covered with approximately 5 lbs. of dry ice at 10:20 hrs. The temperatures at 10:25 hrs were nasopharyngeal (NPT): 3°C; burr hole (BHT): 0.4°C; arterial line: 1°C. The data logger showed an isotherm at -22.6°C.

An isotherm (freezing event) is a period of interrupted temperature descent observed on the time vs. temperature graph of a specimen as the specimen undergoes a phase transition, for example when freezing a liquid to a solid. An isotherm occurs as energy is exchanged to rearrange molecules into the new phase, instead of changing the temperature of the system. In the context of cryonics, an isotherm is undesirable because it is an indicator of ice formation, and therefore incomplete vitrification. The formation of a glassy solid by vitrification, which involves no crystallization, does not express an isotherm.

As a result of working with little sleep, ICE personnel slept for a few hours before driving the patient to Alcor. The patient departed California on T-0 days at 15:30 hrs and arrived at Alcor on T-0 days at 20:35 hrs. The BHT was -79°C upon arrival at Alcor (see the Discussion section).

Cooling to Liquid Nitrogen Temperature

A computer program was used to initiate cryogenic cooldown at 21:36 hrs on T-0 days, plunging to -110°C and descending thereafter at -1°C/hour to liquid nitrogen temperature. At 21:37 hrs neither the primary nor the backup cooldown systems showed any temperature readings. A back-up computer was successfully installed, and cooldown continued (see the Discussion section).

Cooldown was terminated at 20:42 hrs on T+4 days. On T+52 days, CT scans were made of the patient's cephalon, and the

patient was then transferred to long-term maintenance at liquid nitrogen temperature.

Timeline and Time Summaries

TIMELINE

T-0 days	01:43	Estimated time of cardiac arrest
T-0 days	02.08	Pronouncement of legal death
T-0 days	02.00	Start ice bath cooling
T-0 days	02:20	Insert Nasopharyngeal probes
		(estimated,
T-0 days	02:20	Start mechanical chest compression
T-0 days	02:20	Placement of first intraosseous device (IO)
T-0 days	02:22	Admin of first medication (20 g, sodium citrate)
T-0 days	02:34	Placement of second intraosseous device (IO)
T-0 days	02:49	Admin of final medication (200 ml, Decaglycerol/THAM)
T-0 days	04:00	Stop cardiopulmonary support (NPT not recorded)
T-0 days	04:17	Start transport of patient to place of surgery/cryoprotection (funeral home)
T-0 days	04:54	Arrived at funeral home
T-0 days	05:14	Start of field surgery
T-0 days	05:18	Start of cephalic isolation
T-0 days	05:50	End of surgery/cephalic isolation (estimate)
T-0 days	05:52	Weight of cephalon pre-perfusion (4.7 kg)
T-0 days	06:16	Start of open-circuit bladder cryoprotection
T-0 days	10:08	End cryoprotection (final concentration = 51.1 Brix)
T-0 days	10:15	Weight of cephalon post-perfusion (4.9 kg, 4% gain)
T-0 days	10:20	Start of dry ice cooling (NPT =37°C, BHT = 33°C)
T-0 days	15:30	Begin vehicle transport of patient to Alcor
T-0 days	20:35	Arrival of patient at Alcor (see Discussion re temp)
T-0 days	21:36	Start patient cryogenic cooldown
T+4 days	20:42	End of cryogenic cooldown
T+51 days	00:00	CT scans at LN2 temperature
T+51 days	00:00	Transfer of patient to long-term maintenance

Event	ĺ	Dove	Time	
Duration		Days	Time	
(hr:min)				
STABILIZA	TION			
00:25	From:	T-0	01:43	Estimated time of
				cardiac arrest
	Till:	T-0	02:08	Pronouncement of
				legal death
00:37	From:	T-0	01:43	Estimated time of
				cardiac arrest
	Till:	T-0	02:20	Start mechanical chest
00.20			01.42	compression
00:39	From:	1-0	01:43	Estimated time of
	T;11.	ТО	02.22	Admin of first
	1111.	1-0	02.22	medication (20 g.
				sodium citrate)
00:27	From:	T-0	02:22	Admin of first
				medication (20 g,
				sodium citrate)
	Till:	T-0	02:49	Admin of final
				medication (200 ml,
PERFUSIC	N (FCP)		TOPRC	DIECIANI
03:31	From:	T-0	01:43	Estimated time of
				cardiac arrest
	Till:	T-0	05:14	Start field surgery
00:36	From:	T-0	05:14	Start field surgery
	Till:	T-0	05:50	End of surgery/
				cephalic isolation
04.22	E.		01.42	(estimate)
04:33	From:	1 1-0	101.43	Lightermoted terms of
		1.0	01115	cordiac arrest
	T:11.		06.16	cardiac arrest
	Till:	T-0	06:16	cardiac arrest Start of open-circuit bladder cryoprotection
03:52	Till:	T-0	06:16	cardiac arrest Start of open-circuit bladder cryoprotection Start of open-circuit
03:52	Till: From:	T-0 T-0	06:16 06:16	cardiac arrest Start of open-circuit bladder cryoprotection Start of open-circuit bladder cryoprotection
03:52	Till: From: Till:	T-0 T-0 T-0	06:16 06:16 10:08	cardiac arrest Start of open-circuit bladder cryoprotection Start of open-circuit bladder cryoprotection End cryoprotection
03:52	Till: From: Till:	T-0 T-0 T-0	06:16 06:16 10:08	cardiac arrest Start of open-circuit bladder cryoprotection Start of open-circuit bladder cryoprotection End cryoprotection (final concentration =
03:52	Till: From: Till:	T-0 T-0 T-0	06:16 06:16 10:08	cardiac arrest Start of open-circuit bladder cryoprotection Start of open-circuit bladder cryoprotection End cryoprotection (final concentration = 51.1 Brix)
03:52	Till: From: Till: From:	T-0 T-0 T-0 T-0	06:16 06:16 10:08 01:43	cardiac arrest Start of open-circuit bladder cryoprotection Start of open-circuit bladder cryoprotection End cryoprotection (final concentration = 51.1 Brix) Estimated time of
03:52	Till: From: Till: From:	T-0 T-0 T-0 T-0	06:16 06:16 10:08 01:43	cardiac arrest Start of open-circuit bladder cryoprotection Start of open-circuit bladder cryoprotection End cryoprotection (final concentration = 51.1 Brix) Estimated time of cardiac arrest
03:52	Till: From: Till: From: Till:	T-0 T-0 T-0 T-0 T-0	06:16 06:16 10:08 01:43 10:08	cardiac arrest Start of open-circuit bladder cryoprotection Start of open-circuit bladder cryoprotection End cryoprotection (final concentration = 51.1 Brix) Estimated time of cardiac arrest End cryoprotection
03:52	Till: From: Till: From: Till:	T-0 T-0 T-0 T-0 T-0	06:16 06:16 10:08 01:43 10:08	cardiac arrest Start of open-circuit bladder cryoprotection Start of open-circuit bladder cryoprotection End cryoprotection (final concentration = 51.1 Brix) Estimated time of cardiac arrest End cryoprotection (final concentration = 51.1 Brix)

00:36	From:	T-0	05:14	Start field surgery
	Till:	T-0	05:50	End of surgery/
				cephalic isolation
				(estimate)
01:02	From:	T-0	05:14	Start field surgery
	Till:	T-0	06:16	Start of open-circuit
				bladder cryoprotection
04:54	From:	T-0	05:14	Start field surgery
	Till:	T-0	10:08	End cryoprotection
				(final concentration =
				51.1 Brix)
DRY ICE A	AND LIQ	UID N	ITROG	
00:12	From:	T-0	10:08	End cryoprotection
				(final concentration =
				51.1 Brix)
	Till:	T-0	10:20	Start of dry ice cooling
				(NPT = 37°C, BHT = 32°C)
08.27		то	01.42	
08:57	From:	1-0	01:43	cardiac arrest
	T;11.		10.20	Start of dry ico cooling
	1111.	1-0	10.20	$(NPT = 37^{\circ}C BHT =$
				33°C)
18:52	From:	T-0	01:43	Estimated time of
				cardiac arrest
	Till:	T-0	20:35	Arrival of patient at
				Alcor (see Discussion
				re temperature)
01:01	From:	T-0	20:35	Arrival of patient at
				Alcor (see Discussion
				re temperature)
	Till:	T-0	21:36	Start patient cryogenic
				cooldown

Table of Medications Administered

T-0 DAYS

Time of admin not available

MEDICATION	DOSE	PURPOSE
Propofol	200 mg	Anesthetic; reduces cerebral metabolic demand; reduces the theoretic possibility of increased awareness during aggressive CPS.
Sodium citrate	10 - 20 g	Anticoagulant; prevents blood clot formation.
Heparin	50,000 IU	Anticoagulant; prevents blood clot formation.

TIME SUMMARIES

Vasopressin	80 IU total	Vasopressor; increases blood pressure during CPS.				
Minocycline	200 mg	Antibiotic and neuroprotectant				
SMT (S-methyl- isothiourea)	400 mg	Neuroprotectant (iNOS inhibitor); protects the brain from ischemic injury; raises blood pressure.				
Vital Oxy (w/ saline)	70 mL max	Antioxidants: melatonin, vitamin E (D-alpha tocopherol), PBN (alpha Phenyl t-Butyl Nitrone) and anti-inflammatory carprofen.				
Decaglycerol/ THAM	200 ml	Decaglycerol inhibits cerebral edema.				
Streptokinase	25,000 IU	Added to FCP Bladder #1				

Notes:

- 1. The videos of this stabilization were lost. Since the field report is written using the information from the videos, there are no medication administration times for this report. The table above shows the medications and the standard dosages that are on the Full Stabilization Medications Protocol.
- 2. No antacid was administered because the patient was not intubated.

Preferred endpoint is effluent over 49.9 Brix for 1/2 hr

Brix (calc)

Table of Concentrations (Brix) of nM22 Solution

[nM22],

0.00

0.05

0.08

0.14

0.23

0.50

0.5

1.06

1.06

1.06

1.06

1.06

1.06

1.06

CNV

1

3

4

5

6

7

8

9

10

11

12

13

14

END

A-3434 step-ramp, nM22

2-liter bag

labeled

Note: The bladders of pre-mixed concentrations of cryoprotectant are made up in advance and kept on hand. At the time the bladders used on this case were made up the protocol was to have bladder #1 contain only B1 washout solution. It has been learned on recent cases that starting perfusion with a low concentration of cryoprotectant, and not just washout solution, mitigates developing edema in the patient. For this reason, the protocol is now to always start with bladder #2 which does contain cryoprotectant. Since there is still a stock of bladders where there is a bladder marked #1, those perfusions are noted as having been initiated with bladder #2.

Discussion

Standby, Stabilization and Transport

The member's family reported at 01:43 hrs that the member may have gone into cardiac arrest; this time is used in this report for the time of estimated cardiac arrest. ICE instructed the family to notify the on-call hospice nurse. Three members of the ICE team arrived at the member's home at 02:06 hrs. The hospice nurse arrived at 02:18 hrs. The ICE team waited for the hospice nurse to arrive and noted the time of arrival. However, the nurse gave a different time for pronouncement; she stated the time of death would be the time she arrived at the house. When questioned about the accuracy of the time, she stated she was not going to change the time of death.

The videos of this stabilization were lost. ICE personnel do not know how it happened and will be diligent in the future to not let this happen again.

On field cryoprotection cases,
Alcor supplies a kit containing a
body bag to be used as the portable
ice bath. The team placed the ice
around the patient but planned
to add the water and the SCCD
once the body bag was placed at
the funeral home because (1) the
water would have been too heavy,
and (2) the funeral home personnel
were not cooperative and would not
wait for the water or the SCCD to
be added. Given the cooling rate of
this patient, and the relatively poor
CT scans, initial cooling of this
patient was inferior to what could
have been achieved with a regular
portable ice bath and squid. This
body-bag usage policy may need to
be revisited.

The balloon cuff on the King airway malfunctioned. Therefore,

Cryonics	/ 4th	Quarter	2022
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bag started,

hr:min post-

nouncement

3:42

3:58

4:17

4:34

4:59

5:14

5:31

5:46

6:04

6:18

6:32

6:47

7:10

7:31

7:52

pro-

bag started,

hr:min MST

5:00

5:16

5:35

5:52

6:17

6:32

6:49

7:04

7:22

7:36

7:50

8:05

8:28

8:49

9:10

9.2

11.8

13.1

15.3

19.0

29.9

29.9

52.3

52.3

52.3

52.3

52.3

52.3

52.3

bag flow

rate,

ml/min

effluent,

Brix

125

95

118

80

133

118

133

111

143

143

133

87

95

95

50.3

50.3

no airway was used, and CPS proceeded without ventilation. A new airway was placed in the kit when it was prepared for the next case.

The HOBO datalogger did not function. The patient's home was small and crowded. The stabilization kits had to be placed outside on the porch and the surgical and perfusion kits stayed in the rental vehicle on the street, about a block away. While placing the nasopharyngeal probe during the stabilization, the HOBO data logger would not turn on. The team was not aware of the second datalogger in the kit and circumstances did allow time to search for it. For future cases, the team should review availability of spare equipment in the field kit. Temperature probes should be placed in at least two locations (for example, rectal and tympanic) for redundancy.

To further complicate matters, the funeral home personnel were uncooperative and impatient. They had been told that it would take approximately 45 minutes to prep the patient before they could remove the patient and start the transport to the funeral home. They arrived approximately 30 minutes early and were not only annoyed they would have to wait, but they said that they were going to leave, and the cryonics team would have to call them again later, after preparations were finished, causing a significant delay. Additional time and effort went into convincing them to stay. Fortunately, two team members continued to stabilize the patient and, after arrival at the funeral home, a second data logger was found and did function properly.

The burr hole temperature probe was accidentally dislodged from the connector. Field repair to the probe was made. No screwdriver kit was available but surgical tools were used to reestablish the connection.

The burr hole temperature was -79°C upon arrival at Alcor but the burr hole probe had slipped out of the patient upon opening the body bag. It is possible the probe was no longer situated in the burr hole upon arrival.

Field Cryoprotection

The effluent refractive index (RI) readings taken from the jugular vein were not as consistent as experienced on previous cases. To see if the refractometer was malfunctioning, samples were taken from the bladder because the RI of each bladder is always shown on the label. The readings still varied greater than normally expected despite the refractometer being calibrated several times. This resulted in only taking a refractive index reading once, at the start of the 1-hour countdown to termination of cryoprotectant perfusion. To determine the final hour of perfusion, several measurements were taken, and an average (50.3 Brix) was used to determine if the perfusion should be terminated. Alcor personnel checked the refractometer but found it to be functioning normally. The refractometer in the kit has been replaced in case the malfunction was intermittent.

The kit no longer contains a pressure gauge for determining perfusion pressure because it would routinely cause the commercial data loggers to short out and result in loss of data. The pressure transducer devices Alcor uses were built in house to simulate the input of a thermocouple amplifier by generating a linearly related voltage as a function of pressure. This prevents the team from being bogged down with monitoring equipment. With the switch to HOBO loggers these started to feed back into the device in a way that would damage them. Alcor staff elected to remove that component.

Until the Universal Data Logger (UDL) being developed at Alcor is available, the field teams will need to estimate the perfusion pressure by the measured height of the bladders. The estimated height of the bladders on the pole was 36" to 38" which is (36" x 2.054 mmHg per inch of height = 74 to 78 mmHg maximum arterial pressure at the infusion site). The goal is to have the pressure between 70 and 80 mmHg and the bladders can be raised or lowered as needed to optimize flow and for protection of the vasculature.

The gravity feed system for FCP uses a tripod that can be adjusted for height to control the arterial pressure. The premixed cryoprotectant was in a series of bladders with graduated concentrations [measured by the refractive index (RI) in Brix units]. By hanging two bladders with different RI concentrations on a teeter-totter atop the tripod, the bladder with the lower RI runs out and becomes lighter. At the mid-way point, the teeter-totter will allow both bladders to flow, mixing the two concentrations and creating a smoother transition from one concentration to the next. When the bladder with the lower RI runs out, the full concentration of the bladder with higher RI is then flowing exclusively. This process allows for a smoother curve in the increasing concentrations of cryoprotectant.

Unfortunately, the teeter-totter device broke resulting in the loss of the mixing function. Bags were infused one at a time. A new, sturdier design for the teeter-totter device has been developed and will be included in the kits going forward.

Cryogenic Cooldown

At the initiation of cooldown an issue developed both in the primary and the back-up cooldown cart. Neither system showed any temperature readings. An additional back-up computer was successfully installed on the cooldown cart. The cause of this problem was not isolated, but it is possible that a software conflict prevented the temperature module from operating correctly.

S-MIX and CT Scans

The total normothermic equivalent ischemic exposure time of this patient was 04:02 hours, which is a relatively high value for a case with SST. As can be seen in the CT scan below most parts of the brain did not receive the minimum concentration of cryoprotectant to suppress ice formation. The CT scan also does not show CPA-

induced shrinking, which further corroborates that the patient suffered significant ischemic injury prior to cryoprotection.

The most plausible explanation for the poorer CT scan results is that the patient spent a significant period of time at normothermic temperatures prior to the start of procedures, ventilation was omitted during cardiopulmonary support, and initial cooling was poor. The Standardized Measure of Ischemic Exposure (S-MIX) expresses the total ischemic exposure prior to the start of cryogenic cooling as the equivalent duration of normothermic ischemia. An S-MIX of 00:00 (hh:mm) is the ideal case of no ischemic damage. The higher the S-MIX time, the more damage.



S-MIX

Cryoprotection and Temperature Graphs

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0

-100.00

18

12

Time, hours post-arrest

6



Factors that improve the S-MIX, and that are quantitatively accounted for in the below table are: shorter times at higher temperatures, ventilation during cardiopulmonary support (CPS), and oxygenation during blood washout. As calculated below, S-MIX duration for this case is 04:02 hrs.

CT Scans

The post-cryogenic cooldown CT scan was obtained on T+51 days; the patient was at liquid nitrogen temperature (-196°C).



	segment	days	time	post-arrest	T _{naso}	CPS with	washout	S-MIX
event	number	(T+X)	(hh:mm)	(hh:mm)	(deg C)	ventilation	oxygenation	(hh:mm)
circulatory arrest		T-0	01:43	00:00	37.0			
	seg 1		00:37	00:37	-1.0	no	no	00:36
start of ice bath cooling & CPS		T-0	02:20	00:37	36.0			
	seg 2		01:40	01:40	-5.2	no	no	01:19
end CPS		T-0	04:00	02:17	30.8			
	seg 3		00:17	00:17	-0.9	no	no	00:11
start transport to funeral home		T-0	04:17	02:34	29.9			
	seg 4		00:57	00:57	-3.2	no	no	00:31
start field surgery		T-0	05:14	03:31	26.7			
	seg 5		01:02	01:02	-3.6	no	no	00:27
start open-circuit cryoprotection		T-0	06:16	04:33	23.1			
	seg 6		03:52	03:52	-20.1	no	no	00:51
end cryoprotection		T-0	10:08	08:25	3.0			
	seg 7		00:12	00:12	-0.7	no	no	00:01
start dry ice cooling		T-0	10:20	08:37	2.3			
	seg 8		01:13	01:13	-2.3	no	no	00:06
temperature drops to 0 deg C		T-0	11:33	09:50	0.0			
totals			9.50	9.50	-27.0			04:02

The CT scans show a heterogenous distribution of frozen blood and areas with sub-optimal concentrations of M22. Only a few minor areas show evidence of concentrations of M22 necessary for vitrification. ■



Cryoprotectant Distribution (Post-cryopreservation CT scan)

Our Recent Heavy Caseload: How Often Can We Expect This?

By R. Michael Perry, Ph.D.

In the four months from early May through early September of this year (2022), we had *nine human cases* (and several pets too, but here we focus on the human only). It was, needless to say, a *busy* time for us with all the cryoprotections, transports, cooldowns, and the expected barrage of associated operations. (But we "held up" and were able to handle this extra case load, all okay, thanks to a lot of dedicated effort by a few people.) It raises the question of how often we can expect happenings like this.

Work I did in 2015 attempted to address this question, based on an estimate of how many cases to expect per year, and the assumption that the cases occur at random. Long story short, if we start with those assumptions and a reasonable estimate of the expected caseload (about 7 cases per thousand members per year, so 10 cases per year for our current membership of about 1,400) it just doesn't "pencil out." It would take nearly 100 years before we would expect to see this many cases occurring at random in 4 months with this average annual caseload.

The expected "wait time" however, is highly sensitive to the expected number of cases per year. If we increase this number from 10 to 14, for example, the wait time shrinks down to 14 years, with a corresponding increase in the per-year likelihood of the clustering of cases. What is happening may be explained by people tending to sign up when they are seriously ill (or legally deceased, we just had a "last minute" case along with the others). Momentarily, then, there was an overload of members likely to need our services soon, which overwhelmed predictions based on previously determined cases-per-year estimates.

A more thorough investigation of this issue would be worthwhile but is beyond our scope here. Instead, mainly I offer some details of the mathematical model to show how it falls short in accounting for the explosion of cases, with some commentary to suggest how the problem may right itself with time.

First, note that the clustering was really unexpected: in the previous *two* years we only had (depending on how you count) 12 or 14 cases. (The two "extras" are still in storage elsewhere, their release hindered by jurisdictional red tape – another story, another time.) It appears we received a rash of "late in the day" signups, maybe in part because it's just gotten easier to sign up. We go now (for those interested) to the mathematics, which is covered in more detail in the 2015 study.¹

There we assumed as noted that the cases occur randomly, with a frequency that scales linearly with the membership size. We assume each case is time-stamped with its starting time (a point in time rather than an interval). A relevant equation, in which the clustering of cases follows a Poisson distribution, gives the probability p(n, t) of having exactly *n* cases that start in a time interval *t*, as

$$p(n,t) = \frac{\exp(-ct) (ct)^n}{n!},\tag{1}$$

with *c* a constant to be determined, depending on the time unit chosen. Related to this, and actually more useful, is the cumulative probability $p_c(n, t)$ of how often you can expect *n* or more cases in time *t*:

$$p_c(n,t) = \exp(-ct) \sum_{k=n}^{\infty} \frac{(ct)^k}{k!}$$
⁽²⁾

The above can be expressed using the hypergeometric function ${}_{1}F_{1}$, which is more convenient for computation:

$$p_c(n,t) = \frac{\exp(-ct) (ct)^n}{n!} {}_1F_1(1;n+1;ct) \quad (3)$$

(Computations and plotting in the present study were done using Mathematica 12.1.1.) A convenient time unit is the year, with constant c = number of cases per year. In the 2015 study an estimate was obtained of 7 cases per 1,000 members per year, using data covering a 10-year period from 2005-2015. Currently our membership total² is about 1,400 so based on this we should expect about 10 cases per year (c=10; note that this is well in excess of the average case load for 2020-21, giving a more conservative estimate of "waiting time" than would follow if we just used this average.)

Given 4 months or 1/3 of a year, we have ct = 10/3, so, with n = 9, our cumulative probability estimate p_1 is only about 0.7%. To interpret this in another useful way, we note that this probability estimates how likely the clustering (9 or more cases in 4 months) would be in a single year. We then define the "wait time" *y* as the amount of time in years for at least one clustering to occur with 50% probability. This would also equal the 50% probability that the event did *not* occur in this interval. This probability in turn

is $(1 - p_1)^y$, giving y in turn as $\log(.5)/\log(1 - p_1)$. (We could use the natural logarithm here, but the base doesn't matter since it divides out.) The wait time y then works out to about 94 years.

According to this result, the clustering we have seen should not be happening for on the order of a century. If members were radioactive atoms and cases started when the atoms disintegrated but not before, then we should see perfect Poisson statistics in the frequency of clustering. This would follow even if we had a mixture of atoms with varying half-lives, so long as the fractions of different half-lives remained constant with time. The reason for this is that varying half-lives will have corresponding, compensating effects on the average cases per time interval, faster-decaying atoms upping the average and lowering the estimated wait time.

Following this, we could model a mixture of older members with shorter time remaining before cryopreservation (shorter "half-life") and younger members (longer "half-life"). Again, this model might give reasonably accurate predictions if the proportions of younger and older members remained constant (or varied slowly) with time. (The constancy of proportion could accommodate membership growth without serious effect.) The explosion in cases we have just seen may perhaps be explained analogously, in terms of our model, as an anomalous effect that would be observed if there was a sudden, unusual influx of shorter-lived atoms. As these quickly disintegrated, a clustering effect could occur over an unexpectedly short time. If, however, this sort of influx became the norm there should be a corresponding increase in the cases per year so that similar clusterings would be predicted to occur more frequently, giving a shorter wait time.

As an illustration, if we assume 14 cases per year rather than 10, the cumulative probability is about 5%, 7 times the amount before, and the wait time shrinks to about 14 years, about 1/7 that before. Once again, we might expect the percentages of different age groups (and other characteristics affecting lifespan) to stabilize over time. So the model could again become reasonably accurate.



Plot showing expected number of years ("wait time") for 9 Alcor cryopreservation cases to occur, with 50% probability, in a time interval given in months, based on an assumption that cases occur at random with expected frequency of 10 cases per year. For the recent observed example of 9 cases in 4 months the expected wait time is nearly 100 years, suggesting that something beyond the simple random model has been at work, perhaps relating to the fact that many of the cases were very recent signups and in poor health from the start, including a last-minute case.



Plot showing wait times for clustering event (9 cases in 4 months), as a function of cases per year. More cases per year yield smaller wait times, as expected. In particular, an increase from 10 cases to 14 cases shrinks the wait time from 94 years to 14 years.

References

- 1. 1. R. Michael Perry, "Estimating and Forecasting Alcor Resource Requirements: Are Cases Random?" *Cryonics* 36(12) (Dec. 2015), 22-24.
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New Book by Robert A. Freitas Jr.

Cryostasis Revival: The Recovery of Cryonics Patients through Nanomedicine



Cryostasis is an emergency medical procedure in which a human patient is placed in biological stasis at cryogenic temperatures. A cryopreserved patient can be maintained in this condition indefinitely without suffering additional degradation, but cannot yet be revived using currently available technology. This book presents the first comprehensive conceptual protocol for revival from human cryopreservation, using medical nanorobots. The revival methods presented in this book involve three stages: (1) collecting information from preserved structure, (2) computing how to fix damaged structure, and (3) implementing the repair procedure using nanorobots manufactured in a nanofactory - a system for atomically precise manufacturing that is now visible on the technological horizon.

"Robert Freitas is an extraordinary thinker and author whose previous works have been transformational for our ability to visualize the extraordinary capabilities of future medical technology. In Cryostasis Revival, he now puts his prodigious previous knowledge of nanomedicine to the task of envisioning methods for healing those whose injuries challenge even the ultimate limits of future medicine. His illuminating results and new insights will greatly inform debate over, and may even help to resolve, controversies that have persisted for decades." — *Gregory M. Fahy, Ph.D., Fellow, Society for Cryobiology & Executive Director, 21st Century Medicine, Inc.*

"Future repair and revival of damaged cryopreserved tissue has been the subject of speculation for decades. This book by a nanomedicine expert examines the problem in detail far beyond anything ever written before. With more than 3000 references, it's both wide-ranging and intensely specific about diverse technical aspects of the problem. It will surely stimulate much discussion, and be an invaluable resource for thinkers about nanomedical cell repair for years to come." — Brian Wowk, Ph.D., complex systems cryobiologist, Chief Technology Officer, 21st Century Medicine, Inc.

"We now have considerable evidence that cryopreserved patients retain the physical structures encoding memory and personality. For most people, the difficulty lies in understanding how it could ever be possible to repair and revive patients. Leading nanomedicine expert Robert Freitas fills in that gap with admirable and remarkable depth. Cryostasis Revival provides an unparalleled clarification of pathways for researchers to explore in the quest to make human cryopreservation reversible." — *Max More, Ph.D., Ambassador, Alcor Life Extension Foundation*

"Cryostasis Revival is the most magnificent tour de force on cryonics ever done with the signature flair, comprehensive coverage and authoritative style of Robert A. Freitas Jr. It describes all the issues involved in reviving cryopreserved patients: from the philosophical (what is "information theoretic death") to the practical (what damage actually takes place during a cryopreservation) to the technological (how to apply nanotechnology to restore a cryopreserved patient) and more. Nothing else even approaches such a complete and incisive treatment of this life-saving subject. Cryostasis Revival is the book to give anyone who's thinking about cryonics but "isn't sure about the science." — Ralph C. Merkle, Ph.D., Senior Research Fellow, Institute for Molecular Manufacturing

Free electronic book and hardback copies for sale at: https://www.alcor.org/cryostasis-revival or Amazon.com

A Short Commentary on Why We Advocate for the Treatment of Aging

By Reason

Recently, I had the occasion to make one of my very infrequent trips to the emergency room. As always the case to date, I get to walk out afterwards, after a very long period of hurry up and wait. Not everyone is so fortunate. One of the things one tends to find in emergency rooms is old people. So many more of life's slings and arrows become an emergency when one is frail, and old people are increasingly frail. Fall over? Emergency room. Sudden infection? Emergency room. And so on and so forth.

Nurses and doctors are inordinately overworked, and there is a long backstory to this state of affairs in which the American Medical Association, generations of regulators, and hospital owners all play the villain in turn. Emergency rooms are a great place to watch the consequences of this in action. A hospital as an entity is caring in the aggregate. There are formal systems of triage, but a great deal more informal triage based on which of the human wheels are presently squeaking. People fall through the cracks in ways large and small.

Waiting is what one does, largely, in an emergency room. A great deal of waiting. Particularly if one walks in and has every prospect of walking back out again. The older woman across from me in the waiting room did not walk in. She was in a wheelchair, and frail to the point at which walking was out of the question. She was alone. The nurses had wheeled her out at some point after intake, and there she was, waiting like the rest of us. In her case, increasingly unhappy in the stoic, quiet way of the elderly. The nurse had left her bag slung over the back of her wheelchair, in such a way as to be inaccessible to a frail older person, unable to apply the modest amount of strength to turn and lift it over. Trivial for you and me, impossible for her.

It was hard to tell that she was unhappy. It didn't show in her face. But after a few times of noticing that she tried to tug at the bag strap, and with no relative or friend in evidence, left alone, I went over to offer assistance. Perhaps others there might have had I not, but none did. I lifted off the bag, put it carefully in her lap, and left her to it. She rooted around, took out slippers and dropped them to the floor which may as well have been on the other side of the ocean for her, inaccessible, and beyond reach. Then found her phone and started working with it. At least a frail person has that!

Unfortunately that turned out not to be the case. A little while later she caught my attention and asked me to call her house. She was difficult to understand, in part because of accent and the COVID-19 rules that lead to everyone still being masked in hospitals, but any conversation was difficult for her. She did not say much, and was slow with what she did say. It wasn't always clear that she understood me. Still, she gave me a number, and I called it. It was out of service, I told her as much, and she seemed to grasp why it wasn't working for me. She then fumbled with her memory, halftrying variations on the number, but not completing any of them.

I asked about her phone, a modern iPhone. Did she have the number in her address book? The phone had a lock code, the usual panel of numbers to enter. She tried that, as she had been, and the phone promptly locked her out for five minutes. Modern security at work. As we waited for that timer to complete, I talked to her, retrieved her slippers and put them on, as she indicated that this was desired. She did not really respond meaningfully to much else of what I said. At one point, she told me clearly that she did not feel well. I flagged a passing staffer and asked him to find someone, and nothing came of that by the time the phone was accessible again. Caring in the aggregate!

I watched her try to enter the phone code again, and she did it in a way that strongly suggested that she did not recall the code at all, or was perhaps not grasping the nature of the lock screen, entering the numbers in ascending order until the iPhone locked her out again, for longer this time. At that point, I went to find an actual nurse myself, and wouldn't take no for an answer. To her credit, the nurse put away what she was doing and came out to see what could or should be done, and had the good idea to look in the intake records for a phone number to call.

The old woman was wheeled away, and I didn't see her again. I walked out somewhat later, the more fortunate and less agedamaged of the two of us. I am not a physician and cannot diagnose dementia, but aspects of the interaction were those of someone who no longer has the full function of their brain. Just considering the physical, she was frail to the point of being unable to support herself, but that in combination with mental deterioration, leading to no longer being able to recall a phone number or even work a modern phone, is a sobering thing to see. Left on her own, she was helpless, and someone had simply left her there.

Fundamentally, this is why we advocate for greater research into the means to treat aging, to produce rejuvenation therapies based on the most plausible approaches to that goal. No-one should find themselves in the position of the old woman I met in that emergency room, a prisoner of her own old age, a shadow of who she once was, left alone and at the whim of those who cared only when prompted to do so.

Peak Stuff: The Dematerialization of the Economy

By Max More, Ph.D.

56 As the economy grows, we use a growing amount of resources." If asked whether that statement is true probably the vast majority of people would say that it is. You may find it intuitively obvious. Economic growth = more stuff = more resources.

In part 1 of the Getting Better series, I showed that pollution is getting better, not worse. So, a growing economy can be decoupled from pollution. In part 2, I argued that scarcity is not getting worse. Resources can get *less* scarce as the economy grows. But surely, a growing economy must use more materials and produce more stuff, right?

No. Not just in theory but in practice economic growth can be decoupled from growth in the amount of "stuff." The economy can *dematerialize*. We can find many examples of relative *decoupling*, where resource use increases more slowly than economic output. But in some of the most advanced economies we are seeing *absolute decoupling*, where economic growth goes along with shrinking use of resources.

How can this be? In this article, I'm going to show that relative and even absolute decoupling are real. I'll give plenty of examples and lots of numbers that you can check for yourself. I'll look at the different ways in which this "dematerialization" of economies takes place and the forces behind it.

Your Swiss Army phone

Let's start with a familiar example: the smartphone. You may remember a scene in the 1978 *Superman* movie where Clark Kent needs to change into Superman but glances at the new (for the 80s) cut-off telephone booths that provide no privacy. Today, Kent wouldn't be able to find any phone booths of *any* kind. Phone booths are one of the things replaced by mobile phones even before they evolved into smartphones. For all but some professionals the smartphone has replaced the camera and the videocam. We no longer need separate GPS devices like those made by Garmin nor those annoying foldout maps that we wrestled with in the wind.

Depending on your personal habits, your phone may relieve you of the need to own or carry an answering machine, alarm clock, pager, Walkman, Discman, or MP3 Player, calculator, flashlight, handheld gaming device, book or eBook reader, radio, portable audio recorder, TV remote, television, and calendar or personal organizer. A Swiss Army Knife is beaten by today's phones in terms of versatility. Digitization also means we save space by no longer needing cassettes, LPs, or DVDs, and we no longer need to drive to the video store.

A 2018 study quantified the reduction in materials and energy from switching to smartphones. Smartphones can reduce material use by a factor of 300 and standby energy use by a factor of 30. The "embodied energy" in the devices is reduced from 1706 kWh to 75 kWh and weight is reduced from 26 kg to 0.1 kg. [Grubler, 2018]

Decoupling

Many writers and thinkers have assumed that a growing economy inevitably uses a growing amount of resources and imposes an ever-heavier burden on the environment in terms of pollution. You can see this in a statement from the former Intergovernmental Panel on Climate Change (IPCC) chair, Robert Watson, who fears that the "more people we have on the Earth and the richer they are, the more they can demand resources." This view is based on assumptions built into models such as IPAT.

IPAT = Human impact (I) on the environment = population size (P) x income or affluence (A) x technology or amount of pollution per dollar of output (T).

Eco-pessimists and enemies of growth typically assume that the population will continue to grow rapidly. They also assume that all effects of population growth are bad. They further assume that increasing income or affluence inevitably means more use of resources and increased burden on the environment. Finally, they assume that technology, especially that put into use since World War II, is responsible for environmental degradation.

As is becoming increasingly obvious to anyone who pays attention, rapid population growth is not inevitable. As we have seen in previous installments of the Getting Better series, global population growth peaked in the later 1960s and has been declining since. In all of Eastern Europe, Japan, and some of Western Europe, population is actually shrinking. In many more countries in Europe and elsewhere, population growth has slowed so much that it is on the verge of ending and reversing.

The P in IPAT in the future can be expected to be a smaller number in most countries and in the world as a whole later this century. Another point that is often missed is that larger populations bring not only burdens but benefits. These include larger markets and more innovation – especially when population is more concentrated (urbanized). We have also seen a steady decline in poverty around the world even as population grows.

Increasing income and wealth and advancing technology can and increasingly do lead to less impact on the environment and even decreased resource use, as we will see below.

The more modest but still important version of the dematerialization thesis is that of *relative* decoupling: Environmental effects and resource use grow at a rate slower than population or income. We see this happen when agricultural yields grow and when efficiency reduces the amount of energy used per unit of output. Figure 1 illustrates this across four regions, including globally. [See Figure 1]

The more dramatic and remarkable version of the dematerialization thesis is that of *absolute* decoupling: Even if population and consumption increase, the environmental and resource impacts decline.

We are seeing this happening in countries including the USA, the UK, Sweden, Germany, and Denmark. Even twenty years ago, one researcher found that "the value of GDP per pound [USA] rose from \$3.64 in 1977 to \$7.96 in 2000." [Bailey, 2001] As Bailey puts it: "...what people want is not more oil, steel, concrete, plastic, newspapers, and so forth. What they want is heating, cooling, housing, information, communication, and entertainment. How those services get to them is immaterial." This decoupling of increased consumption from resources and environmental impact can be achieved in several ways – dematerialization takes several forms.

Forms of dematerialization

You can categorize the forms of dematerialization in multiple ways. Wikipedia, for instance, cites a source using three categories: Optimize, digitize, and servitize. McAfee [2019] groups dematerialization into four: slim, swap, optimize, and evaporate. As companies seek to maintain and expand their profit margins, they figure out ways of using fewer resources.

They may *slim* by using less of a particular material. Aluminum cans use less metal (25% less for soft drinks and 50% less for food



Figure 1. Recent trends in real GDP, total energy use and total material use for China, Germany, OECD and the World. [Ward, et. al, 2016] cans). You might recall a scene in *Jaws* (1975) where Captain Quint intimidates Hooper by crushing a beer can with one hand – a feat far less impressive today. Farmers are producing bigger harvests with less fertilizer, land, and water. Magnet makers are using fewer rare earth metals. The weight of an average car has fallen by 25% since the 1970s. Communications satellites provide another example: Telstar 1 in 1962 "could handle 600 telephone calls simultaneously. Modern Intelsat satellites can handle 120,000 calls and 3 TV channels at the same time." [Bailey 2001]

Companies may also *swap* by replacing one resource with another. Consider how US coal consumption fell as fracking took off. If we committed to nuclear energy, we could cut back usage of both coal and natural gas. A kilogram of uranium-235 fuel contains about 2-3 million times as much energy as the same mass of coal.

Another path is to *optimize* by making better use of existing materials. McAfee notes that improving CNW's railcar utilization from 5% to 10% would halve the company's stock of 30-ton cars. Commercial airlines have optimized by improving their load factors. The percentage of seats occupied on flights has risen from 56% in 1971 to over 81% today.

The final path is to *evaporate* by replacing some materials with nothing. My smartphone example illustrates this.

Metals

In the United States, there has been a peak then a decline in the consumption of metals, as shown by McAfee. [McAfee, 2019, p.79] Looking at the five most important metals, we can see a reduction not just in annual consumption per capita but a reduction in the total weight of these metals used annually. In other words, all five most important metals in the USA are "post-peak." Peak metal was around 2000. According to the US Geological Survey:

- Copper consumption peaked around 2000 and continued to go down through 2020. Copper consumption fell more than 40% from its peak.
- Aluminum: Consumption down more than 32% from its peak.
- Nickel: Consumption has been up and down but has fallen since 2017.



Figure 2: Absolute use of peaked commodities in the United States from 1900-2010. Uses fiveyear moving average. Data source: USGS National Minerals Information Center (2013).

- Steel: In 2015, US steel consumption was down more than 15% from its high in 2000.
- Gold: Consumption was about the same in 2000 as in 1970. Since 2000, it has continued to decrease.

Figure 2 shows the reduction in the amount of iron ore and pig iron consumed in the United States. A similar reduction is evident for chromium and fluorspar along with much more drastic reductions for sodium sulfate, cadmium, thorium, and asbestos.

Steel has increasingly been replaced with aluminum and its alloys. Cars weigh 30% less than they did sixty years ago. As Smil notes, falling quantities of ore, coal, fluxing materials, and total energy have been used to produce a ton of hot metal, and rising conversion efficiencies in foundries along with the universal adoption of continuous casting mean that steelmaking requires less energy and material.

Another way to see this is to look at the "steel intensity" of the economy over time. This is measured in kilograms per dollar of value produced. "Using constant GDP values adjusted for inflation and expressed in constant 2009\$... the steel intensity of the US economy fell from 37 kg/\$ in 1929 to... 6.7 kg/\$ in 2013." [Smil, 2016]

Even if you adjust apparent domestic consumption numbers for indirectly traded steel-intensive products, you see considerable declines in the absolute numbers. The relative causes vary between countries but include product redesigns and substitution with lighter or cheaper alternatives (mostly aluminum and plastics). In Germany and Japan, less need for building construction also results from static or declining populations.

Peak paper, recovering forests

For years after personal computers appeared, people jeered futurists who forecast the end of paper. It took a few years, but those futurists have been increasingly vindicated. The United States reached peak paper in 1990. Paper usage has been falling ever since even as the population has continued to grow. According to McAfee, "Humanity as a whole probably reached peak paper in 2013." UK researcher Chris Goodall found that paper and board consumption in the UK fell 18% in the decade to 2011. [Pearce, 2011]

Most people probably believe that, in the USA and in Europe, we are losing forest area. The data on the four timber products lumber, plywood and veneer, pulp products, and fuel show that this hasn't been the case for some time. During the last century, a clear trend of relative dematerialization revealed itself. The number of Americans multiplied by 3.5 during the century while US GDP grew nearly fivefold. As Jesse Ausubel points out:

"Had timber consumption risen in constant proportion, Americans would have consumed about 16 times as much timber each year in the 1990s as in 1900, rather than the 1.7 times they actually consumed."

The historical depletion of wood reversed during the last century. The volume of wood on American timberland rose by 36% in the second half of the century. This is partly because the average American consumes much less timber compared to someone in 1900, and partly because millers and foresters became more efficient. You won't hear about it in the news, but many previously cleared areas – such as in New England and the upper Great Lakes states – have regenerated. [Ausubel, 2000]

In a 2015 paper, Ausubel says that foresters talk of a "forest transition" when a country stops losing forested area and starts gaining it. France was the first country, entering forest transition in 1830. Even as the population of France has doubled, so have French forests. As Ausubel puts it: "In other words, forest loss decoupled from population." The United States attained its forest transition around 1950 if you measure by growing stock. Measured by area, the transition was around 1900. [Ausubel, 2015]

Peak commodities

Over the last twenty years or so, Jesse Ausubel in the USA and Chris Goodall in the UK have been tracking signs of dematerialization. In 2011, Goodall found that the amount of physical stuff consumed in the UK had fallen to the level in 1989. That trend has continued since. The country has been consuming less water, building materials, paper, food, cars (automobiles), fertilizers, textiles, and even energy. [Goodall, 2011a; 2011b; 2013; 2014; 2016]

Similar trends are forming across Europe, with reductions in household energy consumption in France, Sweden, and The Netherlands. The use of cars has fallen not just in the UK but also in Germany, Japan, France, Australia, and Sweden.

Following up in 2014 on his 2011 paper, Goodall wrote: "Recent data support the 'Peak Stuff' hypothesis and suggest that economic growth in advanced countries doesn't increase the use of material extracted from the soil or earth's crust." In a 2016 update, Goodall wrote:

"Controversial in 2011, it's now accepted that energy use is also falling across most of the OECD countries and Britain's requirements continue to fall 1-2% a year, even as the economy continues to perform relatively well. Our aggregate use of materials is continuing to fall, as is also the case in the EU as a whole."

Ausubel had noticed that Americans were consuming less per capita. Apart from farmland and timber, he also noticed that use of plastic peaked around 1990. More interestingly, he saw that they were consuming less *in total* of some of the most important components of an economy, such as steel, copper, fertilizer,

timber, and paper. This reversal in use of materials since around 1970 surprised him and intrigued him enough to get together with colleagues to thoroughly examine other trends in the use of 100 commodities in the United States from 1900 to 2010. [Ausubel, 2000, 2008, 2015]

Of the 100 commodities, the researchers found that 36 had peaked in absolute use and another 53 commodities had peaked relative to the size of the economy but were still growing in total. Most of those "now seem poised to fall". At the time of this study, only 11 of the 100 commodities were still growing in both relative and absolute use. In the case of nine basic commodities, absolute use was flat or falling for about 20 years. [Figure 3]

McAfee made a similar finding: "Of the 72 resources tracked by the USGS, only six are not yet post-peak." [McAfee, 2019: 82-83] Gemstones accounted for the great majority of these prepeak resources. Setting aside ornamental stones, "more than 90 percent of total 2015 resource spending in America was on postpeak materials." The one notable non-gem exception is plastic. For several decades, plastic use grew faster than the economy. In recent years, that pattern has reversed and growth in plastic has been lower than growth in GDP.

In other words, despite the growing population of the United States, the intensity of use of resources has begun to fall. A large majority are growing more slowly than GDP and nine basic commodities have been flat or falling in total for around 20 years.

Fertilizers, water, crop acreage

Does Arizona use more or less water today (population 7.3 million) compared to 1960 (when the population was around 1.3 million)? The answer seems obvious. It must be a trick question! No trick but the answer will probably surprise almost everyone: Less. According to the Arizona Department of Water Resources (ADWR), the state used about 7.1 million acre-feet of fresh water in 1957, compared to 7.0 million acre-feet today. [Nicla, 2019]

It's not just Arizona. In the United States as a whole, even as crop tonnage has quadrupled since the 1970s, the amount of



Figure 3: Use of nine basic commodities in the United States from 1900-2010. Uses five-year moving average. Data source: USGS National Minerals Information Center (2013).

water and fertilizer has fallen. In the 1970s, experts predicted increasing water use until 2000 but that is not what happened. Even as the USA grew by 80 million people, water use remained the same. US Geological Survey data shows that water use in 2010 has fallen below the amount used in 1970. Domestic water use in most advanced countries has also declined modestly.

The massive increase in crop tonnage over the last 50 years has been accompanied by a reduction in agricultural area from 472 million to 390 million hectares by the 2010s. Improvements in agricultural productivity have gone hand-in-hand with reductions in acreage also in Europe, Latin America, and East Asia.

Energy

Primary energy consumption in the United States has moved up and down since 1998 but peaked in 2007 at 97 exajoules (97 quintillion joules). In 2019, the number had decreased to 94.65 exajoules. Despite population growth, energy consumption is now lower than in 2000. [Sönnichsen, 2022] In the United Kingdom, primary energy consumption is now lower than it was in 1965. Energy use has stayed steady or declined in other countries such as Sweden, Germany, the United Kingdom, Denmark, and Switzerland. Electricity demand in the UK is the lowest it has been since 1990 (and continues to fall by 1-2% annually) and in Germany since 1999. Across Europe, household energy consumption in 2009 was 9% below the 2000 level. The decline was 15% in France, Sweden, and The Netherlands. These results remain even when you adjust for trade, that is, goods manufactured elsewhere and imported (and the converse).

Even if energy use globally were to continue to rise, the amount of material resources needed to generate it can fall. In 2022, we are finally seeing a long-overdue reawakening of interest in nuclear power (fission, although new results in fusion are also promising). Consider that one kilogram of uranium-235 fuel contains as much energy as 2-3 million times as much coal.

Falling pollutants

I continue to be surprised by how many smart people believe that pollution is getting worse in the USA. In reality, we have seen a decoupling of economic growth from pollution - not just



Figure 4: Primary energy consumption in the USA, 1998-2001. Source: Statistica.

in a relative sense but an absolute reduction in pollution. We can see this clearly by looking at measures of air pollution.

According to the US Environmental Protection Agency (EPA), these are the changes in major pollutants from 1980 to 2018:

- Carbon monoxide down 73%
- Lead down 99%
- Nitrogen oxides down 62%
- Compounds from automobile exhaust associated with ozone down 55%
- Sulfur dioxide down 90%
- Particulates down 61%

Between 1970 and 2017, the combined emissions of six common pollutants (PM2.5 and PM10, SO2, NOx, VOCs, CO, and Pb) dropped by 73%. Aggregate emissions fell 74% from 1970-2018. [EPA, 2018] The trend follows a standard pattern in many countries. Pollutants grew along with population and economic output until the economy reached a certain level of wealth and technology. As Americans continued to become wealthier, a preference for clean air led to continuing reductions in pollutants. The same is true of many other developed countries.

If you consider carbon dioxide to be a pollutant or a problem, note that countries including the USA, UK, France, Spain, Italy, and many others have reduced emissions while increasing GDP. This remains true if we correct for trade. Total CO_2 emissions in the USA in 2020 were the lowest since 1986. Per capita US CO_2 emissions in 2020 were the lowest since 1949 and lower than 1916. The United Kingdom and Sweden have managed even more impressive reductions. Germany's CO_2 emissions per person in 2020 were the lowest since 1950 and similar to the amount in 1912. [Our World in Data, 2020]

Causes of dematerialization

What are the forces driving dematerialization? As McAfee argues, we can first of all dismiss the CRIB strategies: Consume less, Recycle, Impose limits, Back to the land. We have not shrunk our economies. Recycling may have the opposite of the intended effect. When a resource is recycled its price tends to go down because more of it is left. When a resource is cheaper we tend to consume more of it. Rather than going back to the land, we have been doing the opposite. This is good because we put less pressure on the environment and use fewer resources due to greater efficiency.

The two main and interrelated forces leading to dematerialization are capitalism and technology. By "capitalism" I mean a broad term encompassing societies with profit-seeking companies,



Figure 5: Change in emissions compared to growth, population, miles driven, and GDP, 1970-2018. Source: Statistica

strong property rights and contract enforcement, free entry and competition in markets, voluntary exchange, and a high degree of private ownership of property. By this definition, all rich countries today are capitalist. Poorer countries lack these qualities. Much of their economy may be centrally controlled. They may make it hard to start a business, reducing free market entry and competition. Laws may be poorly or inconsistently enforced.

Profit-seeking firms aim to satisfy the boundless wants of people. What people want are goods and services. They do not inherently care how much material they are made of. Profit-seeking firms will always tend to look for more efficient means of providing for wants and needs. To do otherwise would be to ignore an opportunity to profit. Increased profits will be temporary as other firms adopt the innovations and improvements in efficiency. The race then continues as new efficiencies are sought out.

In the pursuit of innovation and efficiency, firms drive technological progress. Government regulation and central direction are not needed and typically get in the way. Markets communicate needs and wants through price signals in a decentralized way that no centralized body can manage. This is not due to just a lack of sufficient computer power. Without markets, accurate information about preferences cannot be gathered and implicit values cannot be made explicit. The inability of a centralized agency to foresee innovations makes it essential to allow and enable markets to create and reinforce incentives to innovate. [Lavoie, 2016] Since "capitalism" in the sense defined here depends on multiple factors, the term can apply to economies that may look quite different. Economic freedom and competitiveness are needed to spur innovation and ultimately dematerialization but these can be measured in various ways. Some people are confused about Scandinavian countries, having the impression that they are socialist or on the socialist end of the capitalism spectrum. Those countries may have larger tax-funded "social safety nets" than the USA but also often have fewer regulations and less central planning.

Although measures of economic freedom differ in their metrics, they usually reveal a very similar picture. The two mostreferenced economic freedom indexes are compiled by the Fraser Institute and the Heritage Foundation. Both give high scores to Singapore, Switzerland, New Zealand, Denmark, Australia, Estonia, and Ireland. They both give very low scores to Democratic Republic of Congo, Algeria, Republic of Congo, Iran, Zimbabwe, Sudan, and Venezuela. [Fraser Institute, 2022; Heritage Foundation, 2022]

Many studies of these relationships have found that countries with higher and improving economic freedom strongly tend to grow faster and generate higher levels of GDP per person. [Figure 6] Economic freedom also correlates with the income share of the poorest 10%, income earned by the poorest 10%, life expectancy, infant mortality, poverty, and other measures of well-being.





Figure 6: Economic Freedom and Income per Capita.

Regulations are often credited with reducing the environmental impact of production. If so, they might also contribute to dematerialization. However, regulations that compel reductions in use of specific resources or in generation of pollutants have costs and side-effects. Regulations have no basis in the preferences expressed in markets and so typically have high costs and unintended consequences.

McAfee's discussion of "responsive government" as a major driver of dematerialization has two major shortcomings. The first is the failure to consider the costs and side-effects of regulations and centrally issued commands. The other, as Adler notes, is the failure to recognize that improvements in environmental measures start *before* regulation. [Adler, 2022] In most cases, it is only when a trend is already underway that regulation is imposed. For instance, the trend toward reduction in pollution started before the EPA. In the seven years before the Clean Air Act, the level of ambient sulfur dioxide fell by 58% in New York. China started doing much better at restraining its carbon dioxide emissions after abandoning communism. [Bailey & Tupy, 2020, p.115]

The future of dematerialization

Will dematerialization continue in the more economically advanced economies? Will dematerialization emerge as other countries become wealthier and more technologically advanced?

Even if the trend does not continue or spread to other countries, we face no shortage of resources – as I have argued in previous installments of the Getting Better series. We will eventually tap resources in our solar system outside of Earth beginning with the Moon and asteroids. The asteroid belt is estimated to contain \$700 quintillion worth of resources. The Davida asteroid is estimated to contain \$27 quintillion of platinum, iron, nickel, and other precious metals. That's \$27,000,000,000,000,000. [Maxey, 2017; Yarlagadda, 2022]

We may not find it necessary or economical to mine the asteroids for a long time if relative and absolute dematerialization continue. Dematerialization does look like an almost inevitable trend – an outcome of the environmental Kuznets curve. [Agarwal, 2022] Named after Simon Kuznets, this curve suggests initial industrialization is a "cheap and dirty" phase where resources are used inefficiently and pollution is extensive but, as a certain level of income is reached, resources are used more efficiently and pollution is reduced. (The original Kuznets curve expressed a similar trend in economic inequality.)

Chris Goodall believes that dematerialization may be accelerating. GDP and resource use are moving beyond relative decoupling to growth with reductions in total material and energy use. Jesse Ausubel notes that it is still the early days, "but Goodall's paper is potentially very significant, and jibes with our work and expectations on dematerialization."



Bucky Fuller and ephemeralization

Perhaps the first person to write about dematerialization was Buckminster Fuller, systems theorist, writer, designer, and inventor (1895-1983), although he called it "ephemeralization", a term he coined in 1927 and discussed in his book, Seven Chains to the Moon. [Fuller 1938] One of Fuller's inventions – the geodesic dome – provides an example of ephemeralization. Compared to standard approaches, the geodesic dome used less material, was lighter, and supported heavier loads.

Fuller used the term to mean the ability of advancing technology to do "more and more with less and less until eventually you can do everything with nothing." According to Fuller, ephemeralization "is the number one economic surprise of world man." The concept referred to increasing efficiency in output of products and services while requiring less effort, time, and resources. Despite finite resources, ephemeralization would result in ever-increasing standards of living for an ever-growing population. Fuller used the example of Washington Carver's assembly line (as used by Henry Ford). Another example is the evolution of bridges. Fuller saw ephemeralization as inevitably affecting all of human development. Markets and technological progress are enabling us to tread more lightly on the planet rather than using it up at an accelerating pace. As Adler puts it, "The Malthusian 'limits to growth' have not merely been delayed or forestalled; they have been transcended."

Looking further into the future, we might also factor in the effects of nanotechnology in whatever forms it takes. The ability to control matter on the atomic level would make reuse and recycling drastically more advanced than it is today. If we move more of our business and personal activity to virtual environments (as these begin to rival physical reality in their richness), fewer physical resources will be needed, with the possible exception of energy to run the computers.

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If we are revived from cryopreservation decades from now, we need not worry that we will inevitably return to a world of poverty, pollution, and desperate scarcity. Far from inevitable, a dark future is unlikely. It is not impossible because the governments of the world might manage to completely block economic and technological progress. Let's not let that happen. ■

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Membership Statistics

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Members a

	Australia
	Austria
	Belgium
S	Brazil
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	United Kingdom

Country

			200							
2022	MAY	JUN	JUL	AUG	SEP	ОСТ	NOV	DEC		
Cryo Members	1380	1384	1389	1392	1393					
Basic Members	5	15	18	19	27					
Patients	191	193	194	198	200					
Assoc./Apps	238	228	239	263	253					
TOTAL	1814	1820	1840	1872	1873					

As a consequence of the transition to a new membership model, complete numbers are only available starting from May 2022 for this year.



TOTAL

Virgin Islands

A Mathematical Model of Infinite Survival

By R. Michael Perry, Ph.D.

Reprinted with minor editing from Abiolysist Macroscope 3 6-9 and 4 4-9 (1986); abstract has been added

Abstract

We consider the problem of indefinitely preserving information based on the assumption that the information is divided into segments called *records*. Each record is subject to radioactive (exponential) decay but also may be copied. It is shown that a slow, logarithmic growth rate in the number of copies is adequate to ensure that the record survives forever with nonzero probability. Such a growth rate, moreover, is sufficient to ensure a similar survival of every record in an expanding hierarchy such as a library or a mind that consists of a growing collection of records, or even a growing collection of record hierarchies of lower order.

Introduction

The survival of an organism such as a human being requires the preservation of the information stored in the brain that encodes the memories and personality. A similar preservation is required for the survival of other entities such as libraries that are devoted to the collection, storage, and retrieval of information. Here we consider the problem of preserving such information based on the assumption that the information is divided into segments called *records*, each of which is subject to radioactive (exponential) decay. Generally speaking, then, records must exist in multiple copies and must be copied repeatedly to insure their survival. Moreover, it is not sufficient merely to maintain a fixed number of copies of a record, but the number of copies itself must grow without limit. It is shown, however, that a slow, logarithmic growth rate in the number of copies is adequate to ensure that the record survives forever with nonzero probability. Such a growth rate, moreover, is sufficient to ensure a similar survival of every record in an expanding hierarchy such as a library or a mind that consists of a growing collection of records, or even a growing collection of record hierarchies of lower order. An expression is derived for the probability of survival increases with the number of copies of the first record that are initially available and decreases with the order of the hierarchy. In fact, under the strategy of record-copying considered, a linear increase in the number of initial copies very nearly offsets a linear increase in the order of the hierarchy, so that corresponding probabilities are replicated.

It should be kept in mind, of course, that the radioactive-decay model of record attrition is not intended as a model of present-day human mortality. Simple record-copying, of the type envisioned here, does not seem an adequate strategy for extending human survival. It should be more relevant to a system to which progressive deterioration such as the aging process does not apply. For the infinite survival of any actual system of records there are issues of a cosmological nature, which are not fully understood, that must also be considered. Some of these are briefly discussed. So, while a definitive answer to the question of whether infinite survival is possible cannot be given, it is hoped that some light has been shed on relevant issues.

An Illustration

A simple example will illustrate the main problem at hand. Imagine you are a librarian in a large, futuristic, heavily-used library that has many rare books found nowhere else but also advanced duplicating equipment from which exact copies of books can be produced as desired. (An alternative would be to assume that the books are stored in a form such as computer disks that lends itself to exact copying with existing technology.) Thus, if copies of a book are depleted through theft, vandalism, etc., they can always be replenished provided at least one copy is still available, though not otherwise. Next, assume for simplicity that the attrition of copies follows the exponential decay law under which, in the absence of replenishing, half the number of copies of a book are lost over a fixed interval of time, the "half-life," say ten years. Until a copy is lost, then, we assume that it has an unchanging probability of attrition in a given time interval, as in the radioactive decay of atoms. (Thus, a copy is either entirely lost or it survives intact.) Next you, as librarian, must conduct periodic inventories and replenish depleted copies of books. Again, for simplicity we assume that the interval between successive replenishings is a fixed fraction (or multiple) of the half-life, say it is the "quarter-life" or time for 25% of the copies to be depleted, in this case about four years.

In replenishing, of course, the number of copies is restored at least to its value at the previous replenishing (or to its initial value). It can be seen, however, that mere replacement of depleted copies in this way, without growth in the number of copies over time, will not be sufficient for infinite survival of the book since there is a nonzero probability that every copy of the book will be lost over a fixed fraction of the half-life. For example, with five copies, there is one chance in 1024 or about 0.1%, that every copy will be lost in one quarter-life. On the other hand, a modest number of copies that are merely replenished and not incremented could result in very long survival times. In the case of the five copies there is about a 50% probability of survival for 709 quarter lives or 2,942 years, and this expected survival time increases exponentially with the number of copies. (The 0.1% attrition rate, of course, would be significant over a much smaller time scale if it applied equally to many different books.) Thus, only a modest growth rate in the number of copies might be adequate to insure infinite survival. In fact, by assuming a logarithmic growth rate we can guarantee infinite survival, as will be shown in the next section.

The Mathematical Problem: Its Formulation and Solution

There are many possible strategies for multiplying copies of books or more generally, records in an information storage-retrieval system. Here we consider a simple strategy which is amenable to mathematical treatment and allows for some growth rates fast enough for infinite survival, and others that are too slow, with an easy characterization of those that are adequate.

Suppose that initially there is some number n>0 of copies of a record, and that a certain fraction, d, is depleted before replenishing occurs. On the *k*th replenishing, then, some number n_k of copies is produced. We assume that $n_k \le n_{k+1} \le n_k+1$, i.e., that n_k is nondecreasing but that at most one new copy is added on any one replenishing. Finally, the increments are assumed to occur only rarely, so that for many consecutive *k* there is no increment, and the intervals between successive *k* at which increments do occur are powers of an integer b>1, the "increment base." To be precise we will assume that there are *n* copies only for the first time interval (n_k for k=0), that is, until the first replenishing occurs, but that there are n+1 copies for the next *b* time intervals, n+2 copies for the next b^2 time intervals, etc. (see table 1, for the case b=2). It can then be shown that n_k is always close to (within 1 of) $n+\log_b(k+1)$, that is, the growth in copies is logarithmic.

We now wish to calculate the probability of infinite survival of the record. The record must survive for every single time interval. Due to the assumption of "radioactive decay," the probability of survival over the *k*th interval of at least one of the n_k copies available is 1 minus the probability that all are lost, or $1-d^{n_k}$. The probability of infinite survival or SP ("survival probability") is the product of the probabilities of survival for each of the individual intervals, that is,

$$SP = \prod_{k=0}^{\infty} 1 - d^{n_k}.$$
⁽¹⁾

However, the n_k are distributed so that for a given value $r \ge 0$ there are precisely b^r values of n_k equal to n+r. On this basis, then, eq. 1 can be represented as

$$SP = \prod_{r=0}^{\infty} (1 - d^{n+r})^{b^r}.$$
 (2)

By substituting values for *n*, *d* and *b* in the above, we can obtain an actual survival probability; for example, if n = 1, d = 0.25, and b = 2 we find that SP = 58.3%. Starting with just one copy of a record then, replenishing every quarter-life, and incrementing the number of copies at intervals equal to powers of 2 times the quarter-life, we obtain better than a 50% probability of infinite survival.

One important question is, when is SP nonzero? This can be shown to occur (for example, by considering the logarithm of the infinite product in (2)) if and only if db < 1. Thus for example, if the copies are only replenished every half-life (d=0.5) but with the same strategy of incrementing the number of copies (b still = 2), there is no probability of infinite survival. The logarithmic growth rate in the number of copies is too slow. (The problem could be corrected, without increasing the frequency of replenishing, by incrementing more often or by allowing increments >1.) This shows that the growth must be at least logarithmic to allow infinite survival.

The foregoing, of course, applies to the case of preserving a single record. The same considerations would hold in the case of a finite number of records; each individually would have to exhibit logarithmic growth in the number of its copies for survival. If all records individually exhibit a nonzero probability of survival, there is also nonzero probability that all will survive. The same cannot be said, however, in the case of infinitely many records. In the next section we consider "record hierarchies" in which the aim is to allow survival of every record of such an infinite class. Again, we will see that logarithmic growth is adequate, provided that the number of starting copies of a given record is suitably chosen; a generalization of eq. 2 will be obtained.

Generalization to Record Hierarchies

To return briefly to our illustration, as librarian you will be concerned with the acquisition of books as well as their preservation. Assume that over unlimited time infinitely many books (records) are to be acquired. It is desirable that no record ever be lost, or in other words, that there be a nonzero probability that every record will survive. For convenience we imagine that the (countably many) records are numbered 0, 1, 2 The *k*th record will be initially present in some number n_{0k} of copies which will be multiplied logarithmically over time so that there will be n_{0k} copies for only one time interval, $n_{0k}+1$ for the next *b* time intervals, etc. For simplicity, then, we assume that all records are multiplied according to the same strategy and only the initial number of copies of a record is varied. The probability that all survive (assuming, as before, that the losses of different copies of records are independent events) is the product of the probability of survival for each record considered individually. This probability in turn must approach 1 as $k \rightarrow \infty$, thus the number of copies n_{0k} must also $\rightarrow \infty$. As it turns out, logarithmic growth in n_{0k} with *k* will be adequate for nonzero survival probability just as it was above for the case involving one record. On the other hand it can be shown that too slow a logarithmic growth rate is inadequate to insure that every record survives even one time interval, let alone forever, so, as in the previous section, the logarithmic growth is the slowest possible that is adequate.

Although different growth rates could be considered, the simplest is just the same rate that is used in the case of individual records, and this, it turns out, will be adequate for infinite survival. That is, we assume that $n_{0k} = n_{00}+1$ for the first *b* values of *k* after 0 ($1 \le k \le b$), $n_{0k} = n_{00}+2$ for the next b^2 values of *k* ($b+1 \le k \le b^2+b$), etc. For convenience we also assume that the first record is present in *n* copies ($n_{00} = n$). In terms of our illustration, we start with *n* copies of the first book, n+1 copies of the next b^2 books, etc. By analogy with eq. 2 we then obtain the survival probability as

$$SP = \prod_{r=0}^{\infty} (1 - d^{n+r})^{(1+r)b^r}.$$
 (3)

This infinite product involves the same factors $1 - d^{n+r}$ as in eq. 2; only the exponents are different and in fact larger. Because of this the survival probability will be lower as expected. In fact on evaluating eq. 3 for the case n=1 we find SP=35.1%. To obtain SP higher than 50% we can choose n=2; the probability then increases to 77.7%. It should be noted that this result does not depend on the actual times of acquisition of the records, provided each individually is multiplied logarithmically over time as indicated. Records, for example, could be acquired at a constant rate or increasingly rarely (provided adequate storage space was available) and the overall probability of survival would be the same.

We have now considered what could be called a record hierarchy of order 0, that is, a single record multiplied over time, as well as a hierarchy of order 1 consisting of a sequence of single records all multiplied according to the same strategy. We now wish to generalize the survival probability to cases of higher-order hierarchies. For example, order 2 would correspond, in our illustration, to a policy of repeatedly setting up branch libraries, each of which is allowed a certain number of copies of the first book, etc. Over infinite time infinitely many such branches would be started, and we want every book of every branch to survive.

In general an *m*th order record hierarchy is constructed by taking a sequence of hierarchies of order m-1. The first of these latter hierarchies starts with *n* copies in its first record, while the next *b* start with n+1 copies, etc. Eqs. 2 and 3 suggest that the survival probability for the *m*th order case, SP(m, n, d, b), has the general form

$$SP = \prod_{r=0}^{\infty} (1 - d^{n+r})^{c_{mr}b^r}$$
(4)

for coefficients c_{mr} . This result can be established inductively, and in fact the coefficients for order *m* are determined from those of the next lower order by

$$c_{mr} = \sum_{s=0}^{r} c_{(m-1)s}.$$
(5)

In this manner, starting with $c_{0r} = 1$, we obtain $c_{1r} = r+1$, $c_{2r} = (r+1)(r+2)/2$, and in general c_{mr} is the binomial coefficient given by

$$c_{mr} = \binom{m+r}{m} = \frac{(m+r)!}{m!r!}.$$
(6)

For purposes of illustration, we would now like to calculate the survival probability for record hierarchies of different orders m and starting values n. A form of eqs. 4-6 that is convenient for computation is derived in the next section, and results of calculations are shown.

Computational Theory and Results

Taking the natural logarithm of the infinite product in eq. 4 and expanding terms according to the Taylor's series

$$-\ln(1-x) = \sum_{k=1}^{\infty} \frac{x^k}{k}$$

gives

$$-\ln(\operatorname{SP}(m,n,d,b)) = -\sum_{r=0}^{\infty} \ln(1-d^{n+r}) \binom{m+r}{m} b^{r}$$
$$= \sum_{k=1}^{\infty} \frac{d^{nk}}{k} \sum_{r=0}^{\infty} \binom{m+r}{m} d^{kr} b^{r} = \sum_{k=1}^{\infty} \frac{d^{nk}}{k} (1-d^{k}b)^{-m-1},$$
(7)

where the last step in the above is obtained from the binomial expansion

$$(1-x)^{-m-1} = \sum_{r=0}^{\infty} \binom{m+r}{m} x^r$$

In particular inspection of eq. 7 shows that the expansion is finite-valued, and consequently SP is nonzero, for the same cases as before, that is, only if db < 1. Again, we see that logarithmic growth in the number of copies, if fast enough, will allow the possibility of infinite survival, but not if too slow, so that, as before, logarithmic growth is the slowest possible that is adequate.

Eq. 7 has two advantages over eq. 4 for computational purposes, (1) much smaller numerical magnitudes are involved, and (2) it is easier to estimate the truncation error obtained by considering only a finite number of terms, consequently, the number of terms that will be needed for a given accuracy. In fact, it is not difficult to show that the error err(p) obtained by truncating the final summation of eq. 7 at k=p for $p\geq 0$ is bounded by

$$\operatorname{err}(p) < \frac{d^{n+p+1}}{(1-d)(1-d^{p+1}b)^{m+1}(p+1)}$$
(8)

with equality holding, asymptotically, in the limit of large p, so that, simplifying the above for this latter case we obtain

$$\operatorname{err}(p) \approx \frac{d^{n+p+1}}{(1-d)(p+1)}.$$
 (9)

We thus obtain linear convergence in the series of eq. 7. No doubt a faster convergence is possible, but this was found adequate for the calculations shown below. It should also be noted that expressions (8) and (9) which give actual magnitudes of error for the logarithmic expression, eq. 7, give the relative error for the quantity SP which is obtained by exponentiation. Thus, if the bound in (8) evaluates to 10^{-6} this corresponds to an error in SP of one part in 10^{-6} or in other words, 6-figure accuracy, a result that is independent of the true value of SP. This accuracy will be exceeded, for all but very large m (m >> 1000) when p=7, or in other words, with 7 terms of summation in eq. 7, for the cases of our illustrations, that is, with d=0.25, b=2.

Table 2 shows some values of the survival probability for a hierarchy of order *m*, starting with *n* copies of the first record, and multiplying copies logarithmically. Inspection of the table shows a rapid drop in SP for fixed *n* and increasing *m*, as expected, and similarly, a strong increase in SP for fixed *m* and increasing *n*. Further inspection shows that the values in SP nearly repeat. We see that the value of SP for a given value of *m* and *n* is nearly the same as for m+2 and n+1, the correspondence improving with increasing *m* and *n*. The reason for this becomes clear by studying eq. 7. It is not difficult to show that, when *n* has the form s(m+1)+t, for $s = \log_d(1-db)$, then SP is approximated by

$$SP(m, n, d, b) \approx \exp(-d^{t}), \tag{10}$$

and in particular,

$$SP(m+s^{-1}, n+1, d, b) \approx SP(m, n, d, b),$$
 (11)

the approximation converging rapidly to exactness with increasing *m* and *n*. In particular, for the case at hand, s = 0.5 or $s^{-1} = 2$ which leads to the observed relation between values shown in the table. Thus, in general, an increase in the hierarchy order *m* is nearly offset by a linear increase in the number of starting copies *n*, so that the survival probability stays almost the same. Another point to note from eq. 10 is that, for fixed, large *m*, SP \rightarrow 1 very rapidly with increasing *n* (that is, *t*>0), but falls to 0 even more rapidly with decreasing *n* (t<0).

<i>n</i> :	1	2	3	4	5	6	7	8	9	10
<i>m</i> :										
0	58.1	88.0	96.9	99.2	99.8	100.	100.	100.	100.	100.
1	35.1	77.7	93.9	98.4	99.6	99.9	100.	100.	100.	100.
2	12.8	60.5	88.2	96.9	99.2	99.8	100.	100.	100.	100.
3	1.72	36.7	77.9	93.9	98.4	99.6	99.9	100.	100.	100.
4	.031	13.5	60.6	88.2	96.9	99.2	99.8	100.	100.	100.
5	.000	1.82	36.8	77.9	93.9	98.4	99.6	99.9	100.	100.
6	.000	.033	13.5	60.7	88.2	96.9	99.2	99.8	100.	100.
7	.000	.000	1.83	36.8	77.9	93.9	98.4	99.6	99.9	100.
8	.000	.000	.034	13.5	60.7	88.2	96.9	99.2	99.8	100.
9	.000	.000	.000	1.83	36.8	77.9	93.9	98.4	99.6	99.9
10	.000	.000	.000	.034	13.5	60.7	88.2	96.9	99.2	99.8

Table 2. Survival probability SP (as %) for record hierarchy of order *m*, starting with *n* copies of the first record and multiplying copies logarithmically. Depletion fraction d = 0.25 and increment base b = 2.

Cosmological Questions

In closing it is worthwhile to briefly consider the possibility of infinite survival in our universe and whether our model of infinite survival would have any validity.

The hierarchy of order 1, which we have likened to a library, can also be compared to a mind, which must store a growing number of records (memories) and must protect each record from loss. A growing community or society of minds would comprise a hierarchy of order 2, and more generally, a hierarchy of order m would be a growing community of hierarchies of order m-1.

Any such phenomenon clearly would require an infinite universe, with an infinite reservoir of negative entropy, something that is not known to exist, though it has not been ruled out. Another issue to consider is how realistic our radioactive-decay model of record attrition is. Clearly it would not be relevant in some situations, such as that involving the aging process, in which the survival of records depends on the overall condition of the organism, something that deteriorates with time. Aging, however, may not prove difficult to treat in the long run. But there are also large-scale destructive effects such as supernovae that make it unclear how far the radioactive-decay model could be trusted. (On a scale still larger than supernovae, however, it could still be valid.) A third issue that would arise in a community of immortals is that of overcrowding.

Would there be enough room for everyone in the end, even supposing the universe is infinite? For example, there could also be infinitely many extraterrestrials all demanding their share of room. While the answer again is not known, even a universe already "full" would not immediately preclude the possibility of infinite survival. An infinite hotel (the "Hilbert Hotel," named after mathematician David Hilbert) can be full and still have a "vacancy." If we move the guest in room 1 to room 2, and similarly, each occupant into the next room, this will vacate the first room and thus allow for one more occupant. By analogy, a universe already "full" could still allow for more individuals. All such beings would be "on the move" to make room for new arrivals. At the same time, larger volumes of space would be constantly required for storing new records or copies of old ones. Both goals might perhaps be accomplished if such beings became increasingly rarefied with time, while at the same time spreading over a larger territory. Such beings could also interpenetrate. It is possible that the known universe is a minor ripple within a far larger, but very tenuous community of beings, which in turn is only the second of an infinite hierarchy of increasingly rarefied organizations of beings, each a tiny ripple in the next. If intelligent life is improbable enough, we could be enveloped in it and still not see it. Perhaps this accounts for the failure to observe extraterrestrials!

In short, we cannot say whether the universe could support infinite survival or whether our model of survival would have long-term relevance. But there seems good reason to think that our universe will at least make it possible to find out. Its known size and stability give at least some grounds for optimism.

The Big Cryonics Survey of 2022

By Max Marty

A smany readers of this publication know, I've had the opportunity to start the Cryonics Underground podcast and the Cryosphere Cryonics Discord community, an online community for discussion of cryonics. My work on those endeavors has given me the opportunity to converse with numerous figures in the community, from the folks who run organizations at the highest levels to those who are new to the concept, and everyone in between. By participating in or observing these conversations, it's occurred to me (and many others) that we cryonicists are a statistically unusual bunch. Relative to the population at large, we seem to hold unusual and unusually strong views about death, the future, the nature of consciousness, truth, conformity, and much else. Some of us claim to be motivated by the longing for adventure or knowledge, others seem motivated by a desire to avoid death or to assuage their anxiety around their eventual and likely demise. Anecdotally, it seems that many of us are programmers, neuro-atypical, irreligious, or have had some other important reasons that compelled us to become early-adopters of this technology.



For all the ways we may be different from the average person, there also seem to be significant differences *between* cryonicists. A great example of one philosophically motivated internal cleavage is our assumptions around destructive mind uploading, with seemingly half of cryonicists believing that destructive mind uploading is (if carried out to a very high degree

of fidelity) perfectly sensible and acceptable to them; the other half of cryonicists being completely opposed to this as a form of revival.

I think it's time for us to stop speculating on these matters and finally have a comprehensive understanding of the minds of our fellow cryonicists. To that end, I've designed and launched a survey that examines these observations with greater rigor than anyone in this community has ever attempted. I'd like to ask everyone to take this survey by pointing their browsers (preferably on desktop, but can also be done on mobile) to:

http://bit.ly/cryosurvey2022

The goal of this survey is to understand what differentiates cryonicists from non-cryonicists, what sorts of internal divisions there are *among* cryonicists on important matters, and to ultimately publish this information (aggregate and anonymized) so that we as a community and the organizations that serve us in this audacious endeavor may find better ways to support our long term goals. The survey is open to all current cryonicists, those who would like to become cryonicists, and those who, for now, merely find the subject interesting. We're also giving away \$100 in prizes to those who complete the survey and can help us come up with helpful ways to market the practice of cryonics to a broader audience. The results will be published in a future issue of this magazine.

Alcor Longevity Circle of Distinguished Donors

The Alcor Board of Directors is pleased to announce the formation of the Alcor Longevity Circle of Distinguished Donors. This new organization will honor those members and their foundations that have donated in excess of \$100,000 over the past few years to support Alcor and its affiliated organizations. In addition to being recognized in Alcor publications and at conferences and other events, members will also be entitled to:

- Exclusive access and a quarterly conference call with Alcor Directors, officers, and officials to get in-depth briefings and ask questions and make suggestions.
- Special recognition, seating, and access to officials at Alcor conferences.
- An exclusive yearly, hosted in-person event honoring members with face-to-face interaction with Alcor Directors, officers, and officials.



• A unique, professionally designed and engraved memento of their membership.

These benefits are, of course, overshadowed by the immense gratitude members' and patients' families will always have for these especially generous individuals. New levels of membership (higher and lower levels of participation) may also be announced in the future.

Support Alcor's **RAPID** Research

Readiness And Procedure Innovation/Deployment (RAPID)

In order to advance the science and reputation of cryonics, Alcor plans to conduct ongoing research to develop novel and near-future products related to cryopreservation procedures and protocols. The RAPID team is developing relationships and contracts to procure recently deceased human cadavers, which are not Alcor members or patients, but are already earmarked for medical research. The idea is to procure one to two cadavers per month to conduct research. We would go on a "light standby" to enable fast access to cadavers.

The RAPID initiative will support cryonics research in multiple ways. Most immediately, it will help advance research into liquid ventilation – using a patient's lungs as a heat exchanger to induce very rapid hypothermia. Animal studies alone cannot take LV development to the next level due to different chest anatomy. LV research will include cooling rate control; chest compression studies; and timing and sensor feedback.

RAPID will also enable research comparing chemical fixation to cryoprotection and will support rewarming studies. Another benefit will be a great improvement in cryonics-specific surgical training. That includes raising and cannulating the carotids; cephalic isolation; raising and cannulating the femoral arteries; field neuro procedure training; median sternotomy training; and alternate surgical approaches.

Alcor is requesting donations through GoFundMe. All donors will receive quarterly reports from Alcor regarding the progress with fundraising and milestone achievements rising from the RAPID program! Please donate today to support Alcor's RAPID initiative. Alcor is a non-profit, federally tax-exempt, 501(c)(3) corporation and your donation may be tax deductible.

Donate here: https://charity.gofundme.com/o/en/campaign/rapid-research/alcorlifeextensionfo

For more information, see the presentation here: https://www.youtube.com/watch?v=BUaVcVMuFWQ&feature=youtu.be

Fight Aging!

Reports From the Front Line in the Fight Against Aging

Reported by Reason

Fight Aging! exists to help ensure that initiatives with a good shot at greatly extending healthy human longevity become well known, supported, and accepted throughout the world. To this end, Fight Aging! publishes material intended to publicize, educate, and raise awareness of progress in longevity science, as well as the potential offered by future research. These are activities that form a vital step on the road towards far healthier, far longer lives for all.

Too Many Epigenetic Clocks, Not Enough Understanding of the Determinants of Epigenetic Age

July 2022

The important point made by the authors of this open access paper is that, in the matter of epigenetic clocks, the focus of the research community should shift from the production of ever more refined clocks that better correlate with chronological age, biological age, or specific manifestations of aging, to attempts to understand how exactly the mechanisms and dysfunctions of aging determine change in these clocks. This is now well understood in most parts of the research community, but it still has to be said, and often.

The real promise of epigenetic clocks, and clocks built on transcriptomic, proteomic, and other similar data, is to make the assessment of potential rejuvenation therapies a rapid and cost-effective process. Simply run the clock before and after the treatment, a very favorable alternative to the lengthy studies that are the only present alternative. Without an understanding of which biological processes the clock reflects, however, that data can't be trusted until that specific clock is calibrated against the specific therapeutic approach with slow, expensive lifespan studies. Perhaps the clock undervalues some mechanisms of aging and overvalues others. At present no-one knows whether or not this is the case for any given clock. This state of affairs is a roadblock for the goal of speeding up the process of research and development.

Epigenetic aging: Biological age prediction and informing a mechanistic theory of aging

Nearly a decade ago, researchers showed that a large number of CpG sites in the human genome increase or decrease in methylation fraction over time, such that one can select among these CpG sites to measure the rate at which an individual ages. These so-called "epigenetic clocks" train regularized linear regression models to predict the chronological age of an individual from the methylation values of CpG sites distributed across the genome. During training, the CpG sites for which the methylation fractions are most predictive of chronological age are identified and selected for use in the linear regression equation. The number of CpG sites selected has depended greatly on the particular approach used but is typically between two and a few hundred.

In the time since these epigenetic clocks were introduced, substantial development effort has been invested into improving their predictive accuracy and extending their range of applications. The first randomized clinical trial using an epigenetic clock as the main validator of intervention efficacy was recently conducted. The prediction of epigenetic age has also been made more accessible and efficient; epigenetic clock software packages are readily available, with some requiring methylation values at only a few CpG sites for accurate age predictions. The sophistication of epigenetic clocks today is greater than it was a decade ago because the tools have broader reach, and we fully expect this trend to continue.

While optimization of existing concepts and methods is important, it is also vital that the field keeps moving. Beyond the construction of increasingly accurate chronological clocks, there are many unanswered questions related to the specific mechanisms by which the epigenome influences aging and, reciprocally, by which aging influences the epigenome. Prediction of age was an important first step, but - in our view - the focus must shift from chasing increasingly accurate age computations to understanding the links between the epigenome and the mechanisms and physiological changes of aging.

Link: https://onlinelibrary.wiley.com/doi/10.1111/joim.13533

Discussing the Accelerated Aging of Cancer Survivors

July 2022

It is well known that cancer survivors who underwent chemotherapy or radiotherapy exhibit a shorter life expectancy, greater chance of unrelated cancer incidence, and greater risk of age-related disease. The most reasonable hypothesis at present is that these undesirable outcomes are the result of an increased burden of senescent cells. Historically, cancer treatments have been in large part designed to force cancerous cells into senescence, those that are not killed outright by the therapy. Since these cancer therapies are toxic to cells, they also tend to cause off-target cell death and senescence. It is possible that similar issues can arise from the more aggressive cancer immunotherapies, but the mechanisms by which the burden of cellular senescence is increased would be very different and more indirect.

This open access paper presents a broad discussion of the ways in which cancer therapies may provoke accelerated aging. It is centered on an increased burden of cellular senescence, but also touches on other hallmarks of aging. Cancer patients should hope that cellular senescence is the primary mechanism by which accelerated aging manifests following treatment, as senolytic treatments capable of selectively destroying lingering senescent cells are under development. Clinical trials to assess whether first generation senolytics (such as the dasatinib and quercetin combination) prevent the increased risk of age-related conditions in cancer survivors would take years to run though to a robust conclusion. It may be possible to get a good idea as to the efficacy of senolytics more rapidly, however, by looking at whether or not they can meaningfully reduce some of the sideeffects of chemotherapy or radiotherapy in the first few months after treatment.

The Achilles' heel of cancer survivors: fundamentals of accelerated cellular senescence

Cancer survivors are at a significantly higher risk of age-related diseases than non-cancer controls, comparable to incident rates in the elderly population. Cellular senescence is a biologic aging hallmark and plays a causative role in numerous age-related diseases, many of which affect cancer survivors. Furthermore, many cancer therapies induce senescence, suggesting that therapy induced senescence (TIS) may be responsible for cancer survivors' various side effects.

A seminal study showed that treating fibroblasts with the chemotherapeutic doxorubicin induces senescence, as indicated by higher SA- β -gal, p16INK4, p21CIP1, and DNA damage response expression. Notably, doxorubicin induces senescence systemically and not only in tumor cells. In addition, doxorubicin significantly impairs hematopoietic stem cell function by

reducing the number of colony-forming units, an effect rescued by ganciclovir-mediated (GCV-mediated) clearance of senescent cells (SCs). Furthermore, cardiomyopathy, a wellknown side effect of doxorubicin, was almost entirely prevented by GCV treatment. Treating mouse breast cancer models with doxorubicin arrests tumor growth, with later cancer relapse, but combining doxorubicin with GCV significantly improves the survival of mice, reduces the incidence of metastasis, and reduces the number of metastatic foci in mice that developed metastasis. Lastly, the nocturnal running time of mice was significantly impaired after doxorubicin treatment, and GCV treatment almost entirely rescued this effect.

Eliminating SCs alleviates many acute effects (elevated inflammatory markers and cardiotoxicity) and chronic effects (fatigue, cancer relapse, metastasis) of doxorubicin, suggesting TIS-dependent pathogenesis of cancer therapy-related adverse effects in survivors, at least those treated with doxorubicin.

Focusing on cellular senescence over other mechanisms assumes that senescence drives accelerated aging processes in cancer survivors while conferring a relatively limited role to other biologic aging hallmarks. This, however, has not been proven; but since transformative preclinical advancements in alleviating age-related health conditions have been achieved by elimination of SCs, we feel it appropriate to focus on cellular senescence and advocate that considering cellular senescence as the driver of early aging in survivors could have great benefits in advancing the implementation of potential cuttingedge interventions to mitigate premature aging.

Undoubtedly, there is a concerted effort from the scientific community to address the phenotypes, mechanisms, biomarkers, and interventions of early aging in cancer survivors. Knowledge about cellular senescence has exponentially increased in recent years on the basis of preclinical studies, but only the outcomes of well-designed, robust clinical studies can prove whether senotherapies will be beneficial in decreasing morbidity, increasing longevity, and improving quality of life in survivors. Thus, the scientific community must go through the rigorous process of translating bench work into clinical trials with a welldefined outcome. Only after completion of randomized trials, if senolytics and other anti-aging drugs show excellent short- and long-term safety and efficacy, should these drugs be used in the clinic.

Link: https://www.jci.org/articles/view/158452

DNA Damage is a Part of Neural Plasticity, Complicating the Study of Its Relevance to Aging in the Brain

As noted by the authors of today's open access paper, there is ample evidence to show that double strand breaks in DNA occur during the normal activity of neurons, such as during the synaptic remodeling necessary to learning and memory. Evolution loves reuse, and few possibilities are ignored! This process of utilitarian double strand breaks appears to be used to ensure that nuclear DNA is spatially reconfigured in such a way as to ensure that certain genes are expressed for a time; recall that the pattern of gene expression at any given moment is very much a function of how the mass of nuclear DNA is packaged, which parts of it, and hence which gene sequences, are accessible at any given time to the machinery of transcription.

This is all very interesting, as stochastic DNA damage, such as double strand breaks, is thought to have a role in degenerative aging. But if the process is taking place on a regular basis during the normal function of neurons, that makes it harder to study in the context of aging and neurodegeneration. On the one hand, DNA damage can spread through tissues from stem cells, and this happens in the brain even given the long-lived nature of neurons. On the other hand, recent research has suggested that the process of repairing repeated double strand breaks can produce some of the epigenetic change of aging as a side-effect, due to depletion of molecules needed to maintain a youthful configuration of nuclear DNA. More research is needed to fill out this presently sparse sketch; important details are missing, and the present understanding of DNA damage in the brain is incomplete.

The Role of DNA Damage in Neural Plasticity in Physiology and Neurodegeneration

DNA damage is now widely implicated in aging and the pathophysiology of age-related neurodegenerative disorders, such as amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), Huntington's disease (HD), and Parkinson's disease (PD). However, emerging evidence suggests that DNA damage and DNA repair are not only induced by pathological conditions. The same processes involved in neurodegeneration as we age are also involved in fundamental physiological functions of neurons that are related to neural plasticity. Hence, DNA damage and repair are associated with neural plasticity, implying an important role for these processes in neuronal function. Furthermore, in neurodegenerative diseases the selective death of specific groups of neurons is present. This suggests that the unique properties of neurons may contribute to selective neurodegeneration in pathophysiology.

Several studies have shown that neuronal activity generates double strand breaks (DSBs) in cultured neurons. A recent study concluded that DSBs are generated physiologically to resolve topological limitations to gene expression in neurons. Topoisomerase enzymes participate in the overwinding or underwinding of DNA and thus they manage DNA topological constraints. Neuronal activity produces DSBs at specific loci in vitro by topoisomerase II β (TopII β), in the promoters of early response genes (ERGs, also called immediate early genes, IEGs) that are crucial for experience-driven changes to synapses, learning, and memory. Interestingly, the expression patterns of ERGs in response to neuronal stimulation correlated well with the formation and repair of activity-induced DSBs, implying that generation of DSBs and their subsequent repair are essential steps for proper gene function. Furthermore, DSBs produced during neuronal excitation were repaired within 2 hours of the initial stimulus, suggesting that this process employs rapid DNA repair mechanisms such as non-homologous end joining (NHEJ).

Dysfunction in these processes of DNA damage and repair is also related to a decline in cognitive function and neuronal death in neurodegenerative diseases. However, human post-mortem tissues represent the end-point stage of the disease. Hence studies examining these tissues cannot be used to determine whether DNA damage has a primary or secondary role in pathogenesis. Future studies on the relationship between plasticity and DNA damage may provide a better understanding of the cellular processes that contribute to higher order brain functions.

Distinct groups of neurons are affected in different neurodegenerative diseases, such as motor neurons in ALS or neurons of the entorhinal cortex in AD, and these cells are specialized to perform specific functions. Given that DNA damage and repair are important for the unique functions of neurons, which in turn depend on their activation, it is possible that the interplay between DNA damage and neural plasticity is unique for specific groups of neurons. This could operate through the activation of specific genes by DNA damage, which would differ depending on the type of neurons involved and their associated functions. Therefore, a better understanding of the interplay between DNA damage and neural plasticity is required, as well as dysfunction in these processes in disease. In particular, the inclusion of specific neuronal types may reveal the causes of selective neuronal death in distinct neurodegenerative diseases.

To date, no previous studies have examined therapeutic strategies directed at DNA damage and repair in relation to aberrant neural plasticity. However, this approach has the potential to identify novel treatments for impaired cognitive functions in neurodegenerative diseases associated with excessive DNA damage.

Link: https://www.frontiersin.org/articles/10.3389/ fncel.2022.836885/full

Are Pharmacological Approaches to Slow Aging in Fact Promising?

August 2022

This open access review paper looks over a selection of what I would consider to be largely unpromising small molecules, each with evidence for their ability to slow aging, but very modestly and unreliably in most cases. Looking at the bigger picture, for much of the public it is still surprising to hear that the pace of aging can be adjusted via any form of therapy, so there is probably a role for simple, low-cost small molecule drugs in the process of education that leads to more serious efforts aimed at producing the means of human rejuvenation. Still, entirely too much effort is devoted towards small molecules that have inconsistent animal data (such as metformin), and also small effect sizes (such as metformin), and further are probably outpaced by the benefits of exercise - metformin again, but near all of the panoply of other calorie restriction mimetics that function via upregulation of cellular stress responses such as autophagy.

There are small molecules that are worth the effort, however. For example, senolytic therapies that selectively destroy senescent cells and produce rapid rejuvenation in animal models. This is far more interesting than the marginal slowing of aging produced by improved cell maintenance, not least because a single senolytic treatment results in lasting improvement as a result of the reduced burden of senescent cells. That said, there is at present a great deal more interest in the research and development community in producing small molecule drugs that alter metabolism to modestly slow aging, which have to be taken continuously over time, and which are unlikely to do better than lifestyle choices. A change in priorities is very much needed if we are to realize the promise of treating aging in our lifetimes.

Pharmacological Approaches to Decelerate Aging: A Promising Path

Aging is the principal risk factor for many illnesses such as cancer, cardiovascular disorders, and neurodegenerative diseases like Alzheimer's disease. Therefore, most elderly are being treated for a variety of chronic diseases and are suffering from side effects of the drugs. Only a 2% hindrance in the progression of aging, compared with treatment of a disabling illness such as cancer would end up to a 10 million rise in healthier individuals and saving a large amount of budget. Hence, identifying smart therapeutic options that uphold the process of aging on one hand and simultaneously cease or decelerate the progression of age-related illnesses is of great significance.

The mTOR inhibitor rapamycin was first identified as an antifungal metabolite. The role of mTOR signaling pathway in longevity and extending of lifespan has been studied in numerous species. In general, inhibition of the mTOR pathway, either genetically or pharmacologically, has shown to increase lifespan in different species. The antiaging effects of rapamycin are exerted through various mechanisms, but the main route of action of rapamycin on the aging process is through inhibition of mTOR pathway. SIRT1 and AMPK occurs following inhibition of mTOR, so rapamycin can also be indirectly effective in the aging process by activating SIRT1 and AMPK following inhibition of the mTOR pathway. As known, mortality rate from infectious diseases is higher in older ages, which may be due to reduced immune function in old ages. One of the mechanisms by which the immune system is rejuvenated is the activation of autophagy. Inhibition of mTOR pathway can increase autophagy and therefore may be effective in increasing immune function during the aging process.

Resveratrol belongs to the polyphenol family exerting medical properties. The antiaging effect of resveratrol is exerted through several mechanisms. Resveratrol mimics the effects of caloric restriction (CR) and shows positive effects of CR in the aging process. It can have antiaging effects by inducing inhibitory effects on inflammation, improving mitochondrial function, suppressing oxidative stress, and regulating apoptosis. Another antiaging mechanism of resveratrol is through the activation of SIRT1. Activation of SIRT1 increases the antioxidant capacity of tissues and improves mitochondrial function.

Metformin is a biguanide and antidiabetic for the first-line treatment of type 2 diabetes. Metformin can lower plasma glucose levels and reduce the amount of glucose absorbed by the body and the amount of glucose produced by the liver. Metformin also enhances tissue sensitivity to insulin. Antiaging effects of metformin are governed by several mechanisms. In general, metformin activates AMPK and inhibits mTOR, downregulates IGF-1 signaling, reduces insulin levels, and inhibits electron transport chain (ETC) and mitochondrial complex 1.

Lithium is an alkali metal that is present in trace amounts in the body. The antiaging effect of lithium may be related to autophagy regulation, increasing telomere length, and enhancement of mitochondrial function in the brain. Inositol monophosphatase (IMPase) and glycogen synthase kinase-3 (GSK-3) contribute to the role of lithium in the regulation of autophagy.

Spermidine is a natural polyamine that is essential for cell proliferation and growth. Spermidine, as a polycation, binds to molecules such as DNA, RNA, and lipids, so it can play an important role in cellular functions. Spermidine affects autophagy, inflammation, DNA stability, transcription, and apoptosis. According to previous studies, spermidine can cause autophagy in multiple organs such as the liver, heart, and muscles. Spermidine induces autophagy by regulating the expression of autophagy-related genes such as Atg7, Atg15, and Atg11. Increased expression of elF5A and transcription factor EB (TFEB) by spermidine also induces autophagy.

Pterostilbene is an analogue of resveratrol from blueberries, which is obtained by both natural extraction and biosynthesis. Pterostilbene has anti-inflammatory, antioxidant, and antitumor effects. In a study investigating the effect of pterostilbene on sepsis-induced liver injury, it was found that pterostilbene activates SIRT1, so it can also affect FOXO1, p53, and NF- κ B. Pterostilbene also decreases the levels of inflammatory cytokines such as TNF- α and IL-6, decreases myeloperoxidase (MPO) activity, and increases Bcl-2 expression. Accordingly, pterostilbene can have anti-inflammatory and antiapoptotic effects.

Melatonin is a hormone in the pineal gland that affects many physiological functions. Melatonin secretion gradually decreases with aging. One of the antiaging mechanisms of melatonin is due to its antioxidant effects and reduction of oxidative stress, which leads to improved mitochondrial function. Melatonin has the ability to scavenge toxic free radicals and decrease reactive oxygen species (ROS) and can indirectly stimulate antioxidant enzymes such as GPx, glutathione reductase (GRd), and SOD. Melatonin also exerts its antiaging effects by increasing SIRT1 expression.

Acetylsalicylic acid or aspirin is obtained from the bark of the willow tree. Aspirin has a variety of medical uses. One of the main uses is to prevent secondary cardiovascular diseases. It also has analgesic and antitumor properties. The antiaging effects of aspirin on C. elegans, mice, and Drosophila melanogaster have been investigated. Lifespan increases when germ cell progenitors become ablated. One of the proposed antiaging mechanisms of aspirin is through its effect on the reduction of germline stem cells. Another proposed mechanism is improving intestinal barrier function by restricting the K63-linked ubiquitination and preventing intestinal immune deficiency.

Fisetin is a natural compound in the category of flavonoids. Fisetin can reduce age-related decline in brain function. This action can also be due to its antioxidant and anti-inflammatory effects. Fisetin can have a direct antioxidant effect and maintain mitochondrial function in the presence of oxidative stress and increase glutathione levels in cells. It also has anti-inflammatory effects against microglial cells by inhibition of 5-lipoxygenase and decreasing the production of lipid peroxides and inflammatory products. Fisetin can prevent neuroinflammation, neurodegeneration, and memory impairment by reducing oxidative stress. These functions are mediated by preventing the accumulation of ROS, inhibiting inflammatory cytokines, and regulating endogenous antioxidant mechanisms. Fisetin has senolytic effects as well by inhibiting the PI3K/AKT pathway. Downstream molecules of the mentioned pathway are involved in different parts of cellular processes by acting on the Akt/ mTOR pathway that eventually leads to elimination of senescent cells. A study in mice found that taking fisetin reduces oxidative stress and inflammation and removes senescent cells; thus, tissue homeostasis is restored and lifespan is increased.

Link: https://www.hindawi.com/journals/omcl/2022/4201533/

Heterochronic Parabiosis in Mice Fails to Extend Lifespan in the Older Animal

August 2022

As practiced in the laboratory, heterochronic parabiosis is the surgical joining of the circulatory systems of an old and young mouse. The older mouse shows signs of rejuvenation, the younger mouse shows signs of accelerated aging. This has led to a great deal of debate and further research into mechanisms; the present weight of evidence favors the improvements in the old mouse to result from a dilution of harmful factors, such as damaged albumin, in the aged bloodstream, rather than by any provision of pro-regenerative factors carried in young blood but not in old blood. Researchers here show that heterochronic parabiosis actually fails to extend life span in the older mice, an interesting addition to the present body of evidence.

A new study in which young and old mice were surgically joined such that they shared blood circulation for three months showed that the old mice did not significantly benefit in terms of lifespan. In contrast, the young mice that were exposed to blood from old animals had significantly decreased lifespan compared to mice that shared blood with other young mice. Heterochronic parabiosis is a research tool used to assess the effect of organs and of blood-borne factors on young and old animals. Less controlled than direct blood exchange, parabiosis is a model of blood sharing between two surgically connected animals.

Researchers used heterochronic parabiosis between young and old mice and the isochronic controls for three months. They then disconnected the animals and studied the effects of being joined on the blood plasma and animal lifespan. "The most robust and interesting result of this study is the fact of a significant decrease in the lifespan of young mice from heterochronic parabiotic pairs. This data supports our assumption that old blood contains factors capable of inducing aging in young animals. Finding and selective suppression of aging factor production in the organism could be the key research field for life extension."

Link: https://home.liebertpub.com/news/can-exposure-toyoung-blood-increase-lifespan/4941

Epigenetic Clocks Do Not Strongly Reflect Inflammatory Status?

August 2022

I recall being surprised by the study from a few years ago showing that early epigenetic clocks are insensitive to physical fitness, as demonstrated in twin studies using fit versus sedentary twin pairs. Given that epigenetic age is higher than chronological age, epigenetic age acceleration correlates with increased mortality, and fitness status is similarly well correlated with mortality, it seems interesting that the machine learning approaches used to generate the clocks from raw epigenetic data by age managed to produce this outcome. This study is similarly surprising, and perhaps more so. It suggests that epigenetic age is not strongly correlated with inflammatory status, and yet it is well demonstrated that increased chronic inflammation in aging drives all of the common age-related conditions, raises mortality risk, and is in general an important component in degenerative aging.

The true promise of epigenetic clocks (and similarly, transcriptomic and other clocks) is to be able to test potential rejuvenation therapies, determining quickly and efficiently whether or not they work, and how good they are relative to other options. As things stand today the research and development communities spend far too much time and effort on marginal therapies. Some process by which poor approaches are cost-effectively winnowed out early on in the development process is very much needed. Ideally, an epigenetic clock measurement would be taken before and after an intervention is attempted, either in mice or in human trials, and provide an unambiguous result. Unfortunately, epigenetic clocks cannot be used in this fashion so long as they have these gaps, unknown until discovered, in which important aspects of aging are not well reflected in epigenetic age.

Inflammation and epigenetic ageing are largely independent markers of biological ageing and mortality

Limited evidence exists on the link between inflammation and epigenetic ageing. We aimed to 1) assess the cross-sectional and prospective associations of 22 inflammation-related plasma markers and a signature of inflammaging with epigenetic ageing; 2) determine whether epigenetic ageing and inflammaging are independently associated with mortality. Blood samples from 940 participants in the Melbourne Collaborative Cohort Study, collected at baseline (1990-1994) and follow-up (2003-2007) were assayed for DNA methylation and 22 inflammationrelated markers, including well-established markers (e.g., interleukins and C-reactive protein) and metabolites of the tryptophan-kynurenine pathway. Four measures of epigenetic ageing (PhenoAge, GrimAge, DunedinPoAm and Zhang) and a signature of inflammaging were considered.

Associations were assessed using linear regression, and mortality hazard ratios (HR) were estimated using Cox regression. Crosssectionally, most inflammation-related markers were associated with epigenetic ageing measures, although with generally modest effect sizes and explaining altogether between 1% and 11% of their variation. Prospectively, baseline inflammationrelated markers were not, or only weakly, associated with epigenetic ageing after 11 years of follow-up. Epigenetic ageing and inflammaging were strongly and independently associated with mortality, e.g. inflammaging: HR=1.41, which was only

slightly attenuated after adjustment for four epigenetic ageing measures: HR=1.35. Although cross-sectionally associated with epigenetic ageing, inflammation-related markers accounted for a modest proportion of its variation. Inflammaging and epigenetic ageing are essentially non-overlapping markers of biological ageing and may be used jointly to predict mortality.

Link: https://academic.oup.com/biomedgerontology/advance-article/doi/10.1093/gerona/glac147/6655953

Discussing the State of the TAME Clinical Trial, Metformin to Slow Aging

August 2022

The TAME clinical trial, still not started, intends to assess the ability of metformin to marginally slow aging in humans. Back at the start of this initiative, it required a long process of negotiation on the part of the trial organizers with the FDA to produce an endpoint that was agreed upon to sufficiently represent aging. To my mind, the TAME trial initiative has already achieved what needs to be achieved: to get the FDA to agree that there is a way to run trials to treat aging. One doesn't actually need to run the trial, and there is in fact little point in running the trial. Metformin is almost certainly a marginal treatment, and attention should be directed instead towards senolytics and other approaches that have much, much better animal data to support their effects on the mechanisms of aging and late life health.

In 2013, Nir Barzilai and two other researchers got a grant from the National Institute on Aging to develop a roadmap to conduct, for the first time in history, a clinical trial that targets aging. They planned to test metformin, a drug that had been approved in the '90s for treating diabetes, and that was shown in epidemiological studies to act against conditions like heart attacks, cancer, and Alzheimer's. It also turned out to be very safe, with few, generally mild side effects. And it's dirt cheap: just six cents per dose.

The biggest obstacle they had was the Food and Drug Administration. The federal regulator adheres to a "one disease, one drug" model of approval. And because the agency does not recognize aging as a disease, there's no path forward for a drug to treat it. And even if there was, it's impractical to do a lifespan study - it would take decades and be astronomically expensive. The solution then would be to use biomarkers as a proxy, as researchers have with other treatments. Barzilai's plan was to launch a new kind of gold-standard trial, designed to prove that the onset of multiple chronic diseases, or comorbidities, associated with aging can be delayed by a single drug: metformin. The ambitious effort aimed to track 3,000 elderly people over five years to see if the medicine could hold off cardiovascular disease, cancer, and cognitive decline, along with mortality.

In 2015, he and a group of academics from more than a dozen top-tier universities met with the FDA to get its blessing for their Targeted Aging with Metformin, or TAME, trial. And to many people's surprise, the agency agreed. All that was left was funding it. Because metformin is a generic drug from which no one could make any money, the trial's sponsor wouldn't be a pharmaceutical company, but AFAR. A trial of the scale researchers were proposing would cost between \$30 million and \$50 million. The National Institutes of Health offered up just a small portion, about \$9 million, toward the difficult but important task of screening for the best biomarkers for assessing if the aging process is actually being slowed. The rest of the money, Barzilai was convinced, could be raised from philanthropists. But despite interest from several people - at one point, Barzilai said, the Israeli American businessman Adam Neumann offered to pay for it all, before his WeWork empire evaporated - the required funds never materialized. "Those big billionaires, they want moonshots, they want a scientific achievement that will make people sav 'wow'. TAME is not a moonshot. It's not even about scientific achievement really, it's more about political achievement. Metformin is a tool to get aging as an indication."

Link: https://www.statnews.com/2022/08/09/anti-aging-projects-funding-much-discussed-trial-overlooked/

Send email to Reason at Fight Aging !: reason@fightaging.org

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Revival Update

Scientific Developments Supporting Revival Technologies

Reported by R. Michael Perry, Ph.D.

Cellular Recovery after Prolonged Warm Ischaemia of the Whole Body

David Andrijevic, Zvonimir Vrselja, Taras Lysyy, Shupei Zhang, Mario Skarica, Ana Spajic, David Dellal, Stephanie L. Thorn, Robert B. Duckrow, Shaojie Ma, Phan Q. Duy, Atagun U. Isiktas, Dan Liang, Mingfeng Li, Suel-Kee Kim, Stefano G. Daniele, Khadija Banu, Sudhir Perincheri, Madhav C. Menon, Anita Huttner, Kevin N. Sheth, Kevin T. Gobeske, Gregory T. Tietjen, Hitten P. Zaveri, Stephen R. Latham, Albert J. Sinusas, Nenad Sestan; *Nature* 608, 405–412, 3 Aug 2022, https://www. nature.com/articles/s41586-022-05016-1, accessed 31 Aug. 2022.

Abstract

After cessation of blood flow or similar ischaemic exposures, deleterious molecular cascades commence in mammalian cells, eventually leading to their death. Yet with targeted interventions, these processes can be mitigated or reversed, even minutes or hours post mortem, as also reported in the isolated porcine brain using BrainEx technology. To date, translating single-organ interventions to intact, whole-body applications remains hampered by circulatory and multisystem physiological challenges. Here we describe OrganEx, an adaptation of the BrainEx extracorporeal pulsatile-perfusion system and cytoprotective perfusate for porcine whole-body settings. After 1h of warm ischaemia, OrganEx application preserved tissue integrity, decreased cell death and restored selected molecular and cellular processes across multiple vital organs. Commensurately, single-nucleus transcriptomic analysis revealed organ- and cell-type-specific gene expression patterns that are reflective of specific molecular and cellular repair processes. Our analysis comprises a comprehensive resource of cell-type-specific changes during defined ischaemic intervals and perfusion interventions spanning multiple organs, and it reveals an underappreciated potential for cellular recovery after prolonged whole-body warm ischaemia in a large mammal.

From: Yale-Developed Technology Restores Cell, Organ Function in Pigs after Death

Bill Hathaway, YaleNews, 3 Aug. 2022, https://news.yale. edu/2022/08/03/yale-developed-technology-restores-cellorgan-function-pigs-after-death, accessed 31 Aug. 2022. Within minutes of the final heartbeat, a cascade of biochemical events triggered by a lack of blood flow, oxygen, and nutrients begins to destroy a body's cells and organs. But a team of Yale scientists has found that massive and permanent cellular failure doesn't have to happen so quickly.

Using a new technology the team developed that delivers a specially designed cell-protective fluid to organs and tissues, the researchers restored blood circulation and other cellular functions in pigs a full hour after their deaths, they report in the Aug. 3 edition of the journal Nature. The research builds upon an earlier Yale-led project that restored circulation and certain cellular functions in the brain of a dead pig with technology dubbed BrainEx. Published in 2019, that study and the new one were led by the lab of Yale's Nenad Sestan, the Harvey and Kate Cushing Professor of Neuroscience and professor of comparative medicine, genetics, and psychiatry.

"If we were able to restore certain cellular functions in the dead brain, an organ known to be most susceptible to ischemia [inadequate blood supply], we hypothesized that something similar could also be achieved in other vital transplantable organs," Sestan said.

In the new study – which involved senior author Sestan and colleagues [David] Andrijevic, Zvonimir Vrselja, Taras Lysyy, and Shupei Zhang, all from Yale – the researchers applied a modified version of BrainEx called OrganEx to the whole pig. The technology consists of a perfusion device similar to heart-lung machines – which do the work of the heart and lungs during surgery – and an experimental fluid containing compounds that can promote cellular health and suppress inflammation throughout the pig's body. Cardiac arrest was induced in anesthetized pigs, which were treated with OrganEx an hour after death.

Six hours after treatment with OrganEx, the scientists found that certain key cellular functions were active in many areas of the pigs' bodies – including in the heart, liver, and kidneys – and that some organ function had been restored. For instance, they found evidence of electrical activity in the heart, which retained the ability to contract.

As in the 2019 experiment, the researchers also found that cellular activity in some areas of the brain had been restored, though no organized electrical activity that would indicate consciousness was detected during any part of the experiment. The researchers stressed that additional studies are necessary to understand the apparently restored motor functions in the animals, and that rigorous ethical review from other scientists and bioethicists is required.

A Compute-in-Memory Chip Based on Resistive Random-Access Memory

Weier Wan, Rajkumar Kubendran, Clemens Schaefer, Sukru Burc Eryilmaz, Wenqiang Zhang, Dabin Wu, Stephen Deiss, Priyanka Raina, He Qian, Bin Gao, Siddharth Joshi, Huaqiang Wu, H.-S. Philip Wong, Gert Cauwenberghs; *Nature* 608, 504– 512, 17 Aug. 2022, https://www.nature.com/articles/s41586-022-04992-8, accessed 30 Aug. 2022.

Abstract

Realizing increasingly complex artificial intelligence (AI) functionalities directly on edge devices calls for unprecedented energy efficiency of edge hardware. Compute-in-memory (CIM) based on resistive random-access memory (RRAM) promises to meet such demand by storing AI model weights in dense, analogue and non-volatile RRAM devices, and by performing AI computation directly within RRAM, thus eliminating powerhungry data movement between separate compute and memory. Although recent studies have demonstrated in-memory matrixvector multiplication on fully integrated RRAM-CIM hardware, it remains a goal for a RRAM-CIM chip to simultaneously deliver high energy efficiency, versatility to support diverse models and software-comparable accuracy. Although efficiency, versatility and accuracy are all indispensable for broad adoption of the technology, the inter-related trade-offs among them cannot be addressed by isolated improvements on any single abstraction level of the design. Here, by co-optimizing across all hierarchies of the design from algorithms and architecture to circuits and devices, we present NeuRRAM - a RRAM-based CIM chip that simultaneously delivers versatility in reconfiguring CIM cores for diverse model architectures, energy efficiency that is two-times better than previous state-of-the-art RRAM-CIM chips across various computational bit-precisions, and inference accuracy comparable to software models quantized to four-bit weights across various AI tasks, including accuracy of 99.0 percent on MNIST and 85.7 percent on CIFAR-1019 image classification, 84.7-percent accuracy on Google speech command recognition, and a 70-percent reduction in image-reconstruction error on a Bayesian image-recovery task.

From: This Mighty Brain Chip Is So Efficient It Could Bring Advanced AI to Your Phone

Shelly Fan, SingularityHub, 30 Aug. 2022, https://singularityhub. com/2022/08/30/this-brain-inspired-chip-ups-ai-computingefficiency-while-using-less-energy/, accessed 30 Aug. 2022. AI and conventional computers are a match made in hell.

The main reason is how hardware chips are currently set up. Based on the traditional Von Neumann architecture, the chip isolates memory storage from its main processors. Each computation is a nightmarish Monday morning commute, with the chip constantly shuttling data to-and-fro from each compartment, forming a notorious "memory wall."

If you've ever been stuck in traffic, you know the frustration: it takes time and wasted energy. As AI algorithms become increasingly complex, the problem gets increasingly worse.

So why not design a chip based on the brain, a potential perfect match for deep neural nets?

Enter compute-in-memory, or CIM, chips. Faithful to their name, these chips compute and store memory at the same site. Forget commuting; the chips are highly efficient work-fromhome alternatives, nixing the data traffic bottleneck problem and promising higher efficiency and lower energy consumption.

Or so goes the theory. Most CIM chips running AI algorithms have solely focused on chip design, showcasing their capabilities using simulations of the chip rather than running tasks on full-fledged hardware. The chips also struggle to adjust to multiple different AI tasks – image recognition, voice perception – limiting their integration into smartphones or other everyday devices.

This month, a study in *Nature* upgraded CIM from the ground up. Rather than focusing solely on the chip's design, the international team – led by neuromorphic hardware experts Dr. H.S. Philip Wong at Stanford and Dr. Gert Cauwenberghs at UC San Diego – optimized the entire setup, from technology to architecture to algorithms that calibrate the hardware.

The resulting NeuRRAM chip is a powerful neuromorphic computing behemoth with 48 parallel cores and 3 million memory cells. Extremely versatile, the chip tackled multiple AI standard tasks – such as reading hand-written numbers, identifying cars and other objects in images, and decoding voice recordings – with over 84 percent accuracy.

While the success rate may seem mediocre, it rivals existing digital chips but dramatically saves energy. To the authors, it's a step closer to bringing AI directly to our devices rather than needing to shuttle data to the cloud for computation.

"Having those calculations done on the chip instead of sending information to and from the cloud could enable faster, more secure, cheaper, and more scalable AI going into the future, and give more people access to AI power," said Wong.

Nucleotide Excision Repair Removes Thymidine Analog 5-Ethynyl-2'-Deoxyuridine from the Mammalian Genome

Li Wang, Xuemei Cao, Yanyan Yang, Cansu Kose, Hiroaki Kawara, Laura A. Lindsey-Boltz, Christopher P. Selby, Aziz Sancar; *PNAS*, 22 Aug. 2022, https://www.pnas.org/doi/full/10.1073/pnas.2210176119, accessed 1 Sep. 2022.

Abstract

Nucleotide excision repair is the principal mechanism for removing bulky DNA adducts from the mammalian genome. including those induced by environmental carcinogens such as UV radiation, and anticancer drugs such as cisplatin. Surprisingly, we found that the widely used thymidine analog EdU is a substrate for excision repair when incorporated into the DNA of replicating cells. A number of thymidine analogs were tested, and only EdU was a substrate for excision repair. EdU excision was absent in repair-deficient cells, and in vitro, DNA duplexes bearing EdU were also substrates for excision by mammalian cell-free extracts. We used the excision repair sequencing (XR-seq) method to map EdU repair in the human genome at single-nucleotide resolution and observed that EdU was excised throughout the genome and was subject to transcription-coupled repair as evidenced by higher repair rates in the transcribed strand (TS) relative to the nontranscribed strand (NTS) in transcriptionally active genes. These properties of EdU, combined with its cellular toxicity and ability to cross the blood-brain barrier, make it a potential candidate for treating cancers of the brain, a tissue that typically demonstrates limited replication in adults.

From: Scientists Discover Surprise Anticancer Properties of Common Lab Molecule

UNC Health (unattributed) 1 Sep. 2022, https://www.unc. edu/posts/2022/09/01/scientists-discover-surprise-anticancerproperties-of-common-lab-molecule/#:~:text=Scientists%20 at%20the%20UNC%20School,fatal%20to%20affected%20cells%2C%20including, accessed 1 Sep. 2022.

Scientists at the UNC School of Medicine have made the surprising discovery that a molecule called EdU, which is commonly used in laboratory experiments to label DNA, is in fact recognized by human cells as DNA damage, triggering a runaway process of DNA repair that is eventually fatal to affected cells, including cancer cells.

The discovery, published in the Proceedings of the National Academy of Sciences, points to the possibility of using EdU as the basis for a cancer treatment, given its toxicity and its selectivity for cells that divide fast.



Nobel laureate Dr. Aziz Sancar at an event in 2016. (Photo by Jon Gardiner/UNC-Chapel Hill)

"The unexpected properties of EdU suggest it would be worthwhile to conduct further studies of its potential, particularly against brain cancers," said study senior author Dr. Aziz Sancar. "We want to stress that this is a basic but important scientific discovery. The scientific community has much work ahead to figure out if EdU could actually become a weapon against cancer."

EdU (5-ethynyl-2'-deoxyuridine) is essentially a popular scientific tool first synthesized in 2008 as an analog, or chemical mimic, of the DNA building block thymidine – which represents the letter "T" in the DNA code of adenine (A), cytosine (C), guanine (G) and thymine (T). Scientists add EdU to cells in lab experiments to replace the thymidine in DNA. Unlike other thymidine analogs, it has a convenient chemical "handle" to which fluorescent probe molecules will bond tightly. It thus can be used relatively easily and efficiently to label and track DNA, for example in studies of the DNA replication process during cell division.

It had been known that EdU is moderately toxic to cells, though the mechanism of its toxicity had been a mystery. The team's findings strongly suggest that EdU kills cells by inducing a runaway process of futile excision repair, which ultimately leads the cell to terminate itself through a programmed cell-death process called apoptosis.

Sancar and colleagues also realized that EdU's properties might make it the basis for an effective brain cancer drug because EdU becomes incorporated into DNA only in cells that are actively dividing, whereas, in the brain, most healthy cells are non-dividing. Thus, in principle, EdU could kill fast-dividing cancerous brain cells while sparing non-dividing, healthy brain cells.

Sancar and his team hope to pursue follow-up collaborations with other researchers to investigate EdU's properties as an anticancer agent.

A Demonstration of Cone Function Plasticity after Gene Therapy in Achromatopsia

Mahtab Farahbakhsh, Elaine J Anderson, Roni O Maimon-Mor, Andy Rider, John A Greenwood, Nashila Hirji, Serena Zaman, Pete R Jones, D Samuel Schwarzkopf, Geraint Rees, Michel Michaelides, Tessa M Dekker; *Brain*, awac 226, 24 Aug. 2022, https://academic.oup.com/brain/advance-article/doi/10.1093/ brain/awac226/6673168, accessed 1 Sep. 2022.

Abstract

Recent advances in regenerative therapy have placed the treatment of previously incurable eye diseases within arms' reach. Achromatopsia is a severe monogenic heritable retinal disease that disrupts cone function from birth, leaving patients with complete colour blindness, low acuity, photosensitivity and nystagmus. While successful gene-replacement therapy in non-primate models of achromatopsia has raised widespread hopes for clinical treatment, it was yet to be determined if and how these therapies can induce new cone function in the human brain. Using a novel multimodal approach, we demonstrate for the first time that gene therapy can successfully activate dormant cone-mediated pathways in children with achromatopsia (CNGA3- and CNGB3-associated, 10-15 years). To test this, we combined functional MRI population receptive field mapping and psychophysics with stimuli that selectively measure cone photoreceptor signalling. We measured cortical and visual cone function before and after gene therapy in four paediatric patients, evaluating treatment-related change against benchmark data from untreated patients (n=9) and normalsighted participants (n=28). After treatment, two of the four children displayed strong evidence for novel cone-mediated signals in visual cortex, with a retinotopic pattern that was not present in untreated achromatopsia and which is highly unlikely to emerge by chance. Importantly, this change was paired with a significant improvement in psychophysical measures of conemediated visual function. These improvements were specific to the treated eye, and provide strong evidence for successful readout and use of new cone-mediated information. These data show for the first time that gene replacement therapy in achromatopsia within the plastic period of development can awaken dormant cone-signalling pathways after years of deprivation. This reveals unprecedented neural plasticity in the developing human nervous system and offers great promise for emerging regenerative therapies.

From: Gene Therapy Partly Restores Cone Function in Two Completely Colorblind Children

University College London (anonymous), ScienceDaily, 24 Aug. 2022, www.sciencedaily.com/releases/2022/08/220824102951. htm, accessed 1 Sep. 2022.

Gene therapy has partly restored the function of the retina's cone receptors in two children who were born completely colourblind, reports a new study led by UCL researchers.

The findings, published in *Brain*, provide hope that the treatment is effectively activating previously dormant communication pathways between the retina and the brain, drawing on the plastic nature of the developing adolescent brain.

The academically-led study has been running alongside a phase 1/2 clinical trial in children with achromatopsia, using a new way to test whether the treatment is changing the neural pathways specific to the cones.

Achromatopsia is caused by disease-causing variants to one of a few genes. It affects cone cells, which (along with rods) are one of two types of photoreceptors in the eyes. As cones are responsible for colour vision, people with achromatopsia are completely colourblind, while they also have very poor vision overall and find bright light uncomfortable (photophobia). Their cone cells do not send signals to the brain, but many remain present, so researchers have been seeking to activate the dormant cells.

Lead author Dr. Tessa Dekker (UCL Institute of Ophthalmology) said: "Our study is the first to directly confirm widespread speculation that gene therapy offered to children and adolescents can successfully activate the dormant cone photoreceptor pathways and evoke visual signals never previously experienced by these patients.

"We are demonstrating the potential of leveraging the plasticity of our brains, which may be particularly able to adapt to treatment effects when people are young."

The study involved four young people with achromatopsia aged 10 to 15 years old, who were taking part in two trials led by Professor James Bainbridge at UCL and Moorfields Eye Hospital, sponsored by MeiraGTx-Janssen Pharmaceuticals.

Each of the four children was treated with gene therapy in one eye, enabling doctors to compare the treatment's effectiveness with the untreated eye.

For two of the four children, there was strong evidence for cone-mediated signals in the brain's visual cortex coming from the treated eye, six to 14 months after treatment. Before the treatment, the patients showed no evidence of cone function on any tests. After treatment, their measures closely resembled those from normal sighted study participants.



Synthetic Embryos Complete Gastrulation to Neurulation and Organogenesis

Gianluca Amadei, Charlotte E. Handford, Chengxiang Qiu, Joachim De Jonghe, Hannah Greenfeld, Martin Tran, Beth K. Martin, Dong-Yuan Chen, Alejandro Aguilera-Castrejon, Jacob H. Hanna, Michael Elowitz, Florian Hollfelder, Jay Shendure, David M. Glover, Magdalena Zernicka-Goetz; *Nature*, 25 Aug. 2022, https://www.nature.com/articles/s41586-022-05246-3, accessed 31 Aug., 2022.

Abstract (Early Access Version)

Embryonic stem cells (ESC) can undergo many aspects of mammalian embryogenesis in vitro, but their developmental potential is substantially extended by interactions with extraembryonic stem cells, including trophoblast stem cells (TSCs), extraembryonic endoderm stem cells (XEN), and inducible-XEN cells (iXEN). Here, we assembled stem-cell derived embryos in vitro from mouse ESCs, TSCs and iXEN cells and showed that they recapitulate whole natural mouse embryo development in utero to day 8.5. Our embryo model displays head-folds with defined forebrain and midbrain regions and develops a beating heart-like structure, a trunk comprising a neural tube and somites, a tail bud containing neuromesodermal progenitors, a gut tube, and primordial germ cells. This complete embryo model develops within an extra-embryonic yolk sac that initiates blood island development. Importantly, we demonstrate that the neurulating embryo model assembled from Pax6 knockout-ESCs aggregated with wild-type TSCs and iXENs recapitulates the ventral domain expansion of the neural tube that occurs in natural, ubiquitous Pax6 knockout embryos. Thus, these complete embryoids are a powerful in vitro model for dissecting the roles of diverse lineages and genes in development. Our results demonstrate the self-organization ability of embryonic and two types of extra-embryonic stem cells to reconstitute mammalian development through and beyond gastrulation to neurulation and early organogenesis.

From: 'Synthetic' Embryo with Brain and Beating Heart Grown from Stem Cells by Cambridge Scientists

Sarah Collins and Jacqueline Garget, University of Cambridge, 25 Aug. 2022, https://www.cam.ac.uk/stories/model-embryo-from-stem-cells, accessed 31 Aug. 2022.

Researchers from the University of Cambridge have created model embryos from mouse stem cells that form a brain, a beating heart, and the foundations of all the other organs of the body - a new avenue for recreating the first stages of life.

The team, led by Professor Magdalena Zernicka-Goetz, developed the embryo model without eggs or sperm, and instead

used stem cells – the body's master cells, which can develop into almost any cell type in the body.

The researchers mimicked natural processes in the lab by guiding the three types of stem cells found in early mammalian development to the point where they start interacting. By inducing the expression of a particular set of genes and establishing a unique environment for their interactions, the researchers were able to get the stem cells to 'talk' to each other.

The stem cells self-organised into structures that progressed through the successive developmental stages until they had beating hearts and the foundations of the brain, as well as the yolk sac where the embryo develops and gets nutrients from in its first weeks. Unlike other synthetic embryos, the Cambridgedeveloped models reached the point where the entire brain, including the anterior portion, began to develop.

This is a further point in development than has been achieved in any other stem cell-derived model.

The team say their results, the result of more than a decade of research that progressively led to more and more complex embryo-like structures and reported today in the journal *Nature*, could help researchers understand why some embryos fail while others go on to develop into a healthy pregnancy. Additionally, the results could be used to guide repair and development of synthetic human organs for transplantation.

"Our mouse embryo model not only develops a brain, but also a beating heart, all the components that go on to make up the body," said Zernicka-Goetz, Professor in Mammalian Development and Stem Cell Biology in Cambridge's Department of Physiology, Development and Neuroscience, adding:

"It's just unbelievable that we've got this far. This has been the dream of our community for years, and a major focus of our work for a decade, and finally we've done it."

Comparative Genomics of Mortal and Immortal Cnidarians Unveils Novel Keys Behind Rejuvenation

Maria Pascual-Torner, Dido Carrero, José G. Pérez-Silva, Diana Álvarez-Puente, David Roiz-Valle, Gabriel Bretones, David Rodríguez, Daniel Maeso, Elena Mateo-González, Yaiza Español, Guillermo Mariño, José Luis Acuña, Víctor Quesada, Carlos López-Otín; *PNAS*, 29 Aug. 2022, https://www.pnas.org/ doi/full/10.1073/pnas.2118763119, accessed 1 Sep. 2022.

Abstract

Turritopsis dohrnii is the only metazoan able to rejuvenate repeatedly after its medusae reproduce, hinting at biological

immortality and challenging our understanding of aging. We present and compare whole-genome assemblies of *T. dohrnii* and the non-immortal *Turritopsis rubra* using automatic and manual annotations, together with the transcriptome of life cycle reversal (LCR) process of *T. dohrnii*. We have identified variants and expansions of genes associated with replication, DNA repair, telomere maintenance, redox environment, stem cell population, and intercellular communication. Moreover, we have found silencing of polycomb repressive complex 2 targets and activation of pluripotency targets during LCR, which points to these transcription factors as pluripotency inducers in *T. dohrnii*. Accordingly, we propose these factors as key elements in the ability of *T. dohrnii* to undergo rejuvenation.

From: The Genetics That Make One Animal Immortal Have Been Revealed

Stephen Luntz, Iflscience, 30 Aug. 2022, https://www.iflscience. com/the-genetics-that-make-one-animal-immortal-have-been-revealed-65101, accessed 1 Sep. 2022.



Turritopsis dohrnii is the only species known to be able to regress to infant stage and regrow again infinitely making it biologically immortal. Image Credit: Maria Pascual-Torner

Immortality exists – but to get it, you need to be a jellyfish, not a god or a vampire. Moreover, only one species of cnidarian, *Turritopsis dohrnii*, is known to have found the secret of eternal life. Geneticists hope comparing *T. dornii*'s DNA with its close relative, *T. rubra*, will help us understand the aging process and how to evade it.

Turritopsis are warm water jellyfish half a centimeter (0.2 inches) long. At least three species of hydra have the capacity to age backwards like Benjamin Button, going from adult to juvenile stage, before eventually growing up again. However, two of these can only go from the hydra equivalent of adolescent to child; like the victim in some uncensored fairytale, sexual reproduction locks them into adulthood. *T. dohrnii*, on the other hand, appears able to go from its free-floating adult stage to bottom-living polyp, known as life cycle reversal (LCR), as many times as it wants.

A paper in the journal *Proceedings of the National Academy of Sciences* provides a comparison of *T. dorhnii* and *T. rubra* in the hope the differences will prove enlightening, throwing in a few more distantly related types of cnidarians as well.

Dr. Maria Pascual-Torner of Universidad de Oviedo, Spain, and co-authors didn't find any single genetic trick that appears to provide the fountain of youth. Instead, they discovered a wide variety of potential contributors, reporting; "We have identified variants and expansions of genes associated with replication, DNA repair, telomere maintenance, redox environment, stem cell population, and intercellular communication."

All of these could eventually prove important, but the study homed in on two significant aspects of *T. dohrnii*'s genome absent in its relative. One of these silences the polycomb repressive complexes: 2 families of proteins that regulate gene expression. The other activates pluripotency – the capacity of a stem cell to turn into whatever sort of cell it needs to become – during life cycle reversal.

Applying these to humans will certainly be a Herculean task if it's possible at all. However, while many of *T. dorhnii*'s features probably only work in combination, some might provide a few precious extra years of health in more complex creatures, ourselves included. ■

A Roadmap to Revival

Successful revival of cryonics patients will require three distinct technologies: (1) A cure for the disease that put the patient in a critical condition prior to cryopreservation; (2) biological or mechanical cell repair technologies that can reverse any injury associated with the cryopreservation process and long-term care at low temperatures; (3) rejuvenation biotechnologies that restore the patient to good health prior to resuscitation. OR it will require some entirely new approach such as (1) mapping the ultrastructure of cryopreserved brain tissue using nanotechnology, and (2) using this information to deduce the original structure and repairing, replicating or simulating tissue or structure in some viable form so the person "comes back."

The following is a list of landmark papers and books that reflect ongoing progress towards the revival of cryonics patients:

Jerome B. White, "Viral-Induced Repair of Damaged Neurons with Preservation of Long-Term Information Content," Second Annual Conference of the Cryonics Societies of America, University of Michigan at Ann Arbor, April 11-12, 1969, by J. B. White. Reprinted in Cryonics 35(10) (October 2014): 8-17.

Michael G. Darwin, "**The Anabolocyte: A Biological Approach to Repairing Cryoinjury**," Life Extension Magazine (July-August 1977):80-83. Reprinted in *Cryonics* 29(4) (4th Quarter 2008):14-17.

Gregory M. Fahy, "A 'Realistic' Scenario for Nanotechnological Repair of the Frozen Human Brain," in Brian Wowk, Michael Darwin, eds., Cryonics: Reaching for Tomorrow, Alcor Life Extension Foundation, 1991. Ralph C. Merkle, "**The Molecular Repair of the Brain**," Cryonics 15(1) (January 1994):16-31 (Part I) & Cryonics 15(2) (April 1994):20-32 (Part II).

Ralph C. Merkle, "Cryonics, Cryptography, and Maximum Likelihood Estimation," First Extropy Institute Conference, Sunnyvale CA, 1994, updated version at http://www.merkle.com/cryo/cryptoCryo.html.

Aubrey de Grey & Michael Rae, "Ending Aging: The Rejuvenation Breakthroughs That Could Reverse Human Aging in Our Lifetime." St. Martin's Press, 2007.

Robert A. Freitas Jr., "Comprehensive Nanorobotic Control of Human Morbidity and Aging," in Gregory M. Fahy, Michael D. West, L. Stephen Coles, and Steven B. Harris, eds, The Future of Aging: Pathways to Human Life Extension, Springer, New York, 2010, 685-805.

Chana Phaedra, "**Reconstructive Connectomics**," Cryonics 34(7) (July 2013): 26-28.

Robert A. Freitas Jr., "The Alzheimer Protocols: A Nanorobotic Cure for Alzheimer's Disease and Related Neurodegenerative Conditions," *IMM Report* No. 48, June 2016.

Ralph C. Merkle, "**Revival of Alcor Patients**," Cryonics, 39(4)&39(5) (May-June&July-August 2018): 10-19, 10-15.

Robert A. Freitas Jr., "Cryostasis Revival: The Recovery of Cryonics Patients through Nanomedicine," Alcor Life Extension Foundation, 2022 (https://www.alcor.org/ cryostasis-revival/)

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The Alcor Life Extension Foundation is the world leader in cryonics research and technology. Alcor is a non-profit organization located in Scottsdale, Arizona, founded in 1972. Our website is one of the best sources of detailed introductory information about Alcor and cryopreservation (www.alcor.org).

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