Biology 215, *Biochemical Evolution*, Fall 1991

Ward Watt

TTh 08:35-09:50, Bio G(ilbert) 117

My office hours are W 1:30-3:00, my office is Bio R 488 THIS WEEK but will be G ~~[illegible]~~ 406A, my phone is 723-4297.

The graded work of the course is a ~20 pp. literature review and synthesis paper. It is due 3 December 1991, which is the next-to-last class meeting and is the Tuesday of "Dead Week". I'd like a brief written statement of choice of paper topic from each class member by 22 October – by all means see me outside class to talk about paper topics before then.

I have to miss scheduled class on 17 October, as I am flying east for the memorial service for for G. E. Hutchinson, who died late last spring at age 88 – still working, we should all do so well! But you should be thinking about when it is convenient for you to make up that class meeting – in the early evening (7:30-9 PM), or some Saturday morning.

The course is not a stereotypic, integrated "package" – the subject matter of the course has not yet been integrated by *anyone* into a fully cohesive whole. Indeed, the aim of the course is to bring together, for our joint consideration, what is an incredibly scattered literature. As a result, there is no textbook, since there is none suitable, and the course works from a reserve shelf, and beyond that from the primary literature. Much of the class meeting time will necessarily be presentation by me, but I earnestly hope that we can get substantive discussion of many different specific topics. That will depend on course members being conscientious about using the reserve shelf! I will try to give some advance warning of key references, but there's nothing like a certain amount of "creative browsing" as well.

While the course is not a "package", it does have an organizing rationale. I will spend parts of two class meetings in review of contemporary evolutionary concepts and contemporary physical/chemical concepts that we'll come back to again and again in one way or another. We'll then look at three very major areas, *not* necessarily giving equal time to each, with a diversity of subtopics within each:

I. Origins of life, or the rise of Darwinian systems out of their pre-Darwinian physical and chemical underpinnings.
- a) Origins of the planet and the solar system; Hadean/Archaean conditions, abstractly and concretely; predispositions and constraints to living chemical systems in the phenomena of physics and in the periodic table
- b) Palaeontological constraints on explanations: the microbial fossil record
- c) Bio-monomer formation under simulated Hadean/Archaean conditions
- d) The problem of polymer formation
- e) The origins of catalysis
- f) The origins of the genetic code and the general problem of cellular self-assembly; the transition from pre-biotic to proto-biotic systems.

II. Mechanistic/ biochemical perspectives on Darwin's global problem # 1: The origins and improvement of adaptation to environmental pressures
- a) Fitness-related measures for metabolic performance
- b) Evolution of metabolic pathway choice
- c) Evolution of metabolic kinetic organization
- d) Evolution of enzyme/protein structure, and population genetics of contemporary enzyme/protein variation

III. Mechanistic/ biochemical perspectives on Darwin's global problem # 2: The origins, increase, and maintenance of phyletic diversity

a) Evolution of gene families over time
b) Interaction of adaptive and phyletic evolution -- how are they related, if at all?
c) Local phyletic history by sequence comparisons
d) "Deep" phyletic history by sequence comparisons, including endosymbiotic explanations for the eukaryotic cell structure strategy

General references

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Margulis, L., and K.V. Schwartz. *Five kingdoms*, ed. II.
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9·26·91
Bro. 215

Biochemical Evolution

Darwin - Origin of Species

① Evolution by natural selection
- population genetics

has led to

Adaptation ⟷ **Phyletic differentiation** — how explain these two? " " their interaction?

- comp. biochem
- physiological ecology
- molecular systematics

So - have these been explained?

Transmission of genotypes

- even diploid organisms can only transmit "haploid" cells
- this severely constrains the possibilities for evolution.

Evolution by natural selection

genotypes ▲■●

→ (environment) →

phenotypes ▲■● ⟷ environment (filter)

→ biological performance ▲■●

→ demographic performance ▲■●
l_x = survivorship
m_x = reproductive output

$R_{■}, R_{●}, R_{▲}$ ← demographic performance

W_{ij} — change in gene frequency (population genetics) → genotypes

$\Sigma l_x m_x$ or $\int l_x m_x = R$ · "net repro rate"

- can determine genotypic specific "R", a.k.a. $R_{▲}, R_{■}, R_{●}$ = relative fitness

Take $R_{\blacktriangle}$, $R_{\blacksquare}$, $R_{\bullet}$ and refer to reference "R" to get relative fitness value.

$W_{ij} = \frac{R_i}{R_j}$: relative fitness of genotypes

<u>Transmission of genotypes</u>

$$\Delta p_i = \frac{p_i(\Sigma p_j W_{ij} - \overline{W})}{\overline{W}} + \mathcal{E}_{f(1/N_e)} \quad \overline{W} = \Sigma W_{ij} p_{ij}$$

= error term to include drift, inbreeding

~~prob.~~ p = percent of genotype

<u>Problems</u>-

Genetic Load Controversy

~~J~~BS Haldane; said that for a new allele to enter pop.; some organisms carrying old allele should die. ∴
∴ things can't change much too fast.

How much constraint is there on evolution?
- historical accident
- opportunism (aka. preadaptation)

How predictable is evolution?
- depends on scale
- how predictable is environment?
- CONVERGENCE suggests predictability

How do adaptation & phyletic differentiation interact?

① GG Simpson
- adaptive zone (also - Hutchinsonian niche or applying fitness values to environmental gradients)

② [illegible]

CONVERGENCE

- interaction between clade's & grades

→ Hawk Moth & Hummers: v. similar "grades" but v. diff clades

10·3·91
Bioch. Evol.
Bio 215

<u>Thermodynamics & Kinetics</u> - looking for analogs to <u>Darwinian parameters</u>

adaptation to environ

↓

performance

↙

fitness

- how did Darwinian systems originate in Prebiotic systems?

1st Law ① Conservation of mass/energy

2nd Law ② Systems move from high → low E

$$\underset{\text{Gibbs free energy}}{\Delta G} = \underset{\text{enthalpy}}{\Delta H} - T\underset{\text{entropy}}{\Delta S}$$

$\Delta G < 0$ for spontaneous process

~~: enthalpy~~

~~ΔH~~	~~ΔS~~	
−	− ($\Delta S = +$)	explosion
+	~~+~~ ($\Delta S = ++$)	ice cream
−−	+ ($\Delta S = -$)	nylon

- so an incr. in complexity must be associated with a decrease in enthalpy

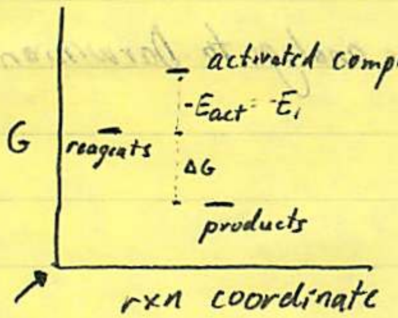
- so -- how do you get to a system w/ enough order and/or complexity to become Darwinian

<u>Equilibrium</u>

$$K_{eq} = e^{(-\Delta G/RT)}$$

$$\Delta G = -RT \ln K_{eq}$$

<u>but</u> doesn't say anything about rate -- bec. no info about <u>activation</u>



A = collision frequency

$K = Ae^{-E_{act}/RT}$ $k_f = Ae^{-E_1/RT}$ = forward rate constant

$k_b = Ae^{-(E_1+\Delta G)/RT}$

K_{eq} does <u>NOT</u> relate to rate -- just ratios

<u>Important Parameters</u>

① <u>Efficiency</u>

$E = \frac{O}{I}$ ∴ high $E \rightarrow \Delta G$ is small

② <u>Yield</u> $Y = E \cdot K_{eq}$ if $K_{eq} = 1$ then $O = I$ & $Y = 50\%$

③ <u>Net yield</u> if $K_{eq} =$

Non-Equilibrium

- e.g. $[H^+]$ gradient in Chloroplasts $\frac{[H^+]_{high}}{[H^+]_{low}}$

① Near-Equilibrium — Lars Onsager

e.g. Popcorn…
- oil forms convection currents
- entropy decreases
- maintained by flow of energy

- continuous input of energy can maintain "order"

② two flows

$J_1 = L_{11}X_1 + L_{12}X_2$

$J_2 = L_{21}X_1 + L_{22}X_2$

J_n = flow
L_{nn} = coupling constant
X_n = force driving flows

- to get a linear relationship betw. J & X

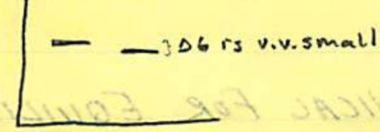
ⓐ $\Delta G \ll RT$ because $\Delta G/RT$ is exponent

$\therefore \Delta G/RT \cong 0 \quad e^0 = 1 \quad \therefore$ linear

- RT at 0°C = 2.27 kJ/mol ≅ 0.5 kcal/mol

except e.g.
$2ADP \xleftrightarrow{Ad.Kinase} ATP + AMP$

∴ cannot break too many chemical bonds…
better if no chemical change



ⓑ energy can approximate rate if ($\Delta G \ll RT$)
the system is near-equilibrium

ENTROPY $T\Delta S \approx$ information (is proportional to)

BOLTZMAN ① $S = k \ln W$ = W = # of equally probable ~~microstate~~ microstate that a macrostate can be in.

e.g.: two dice
- total = macrostates = 11

2×1	2
2×2	= 4
2×3	= 6
2×4	8
2×5	= 10

2,12 = 1 microstate = 1/36
~~2~~,3,11,~~10~~ = 2 = 1/18
7 = 6 microstates = 1/6
4,10 = 3 = 1/12 (22 31)
5,9 = 4 = 4/9 (37 51 15)
6,8 = 5 = 5/36

= ~~k p ln p~~ $-K \sum p_i \ln p_i$

1,1	21	31	41	51	61
12	22	32	42	52	62
13	23	33	43	53	63
14	24	34	44	54	64
15	25	35	45	55	65
16	26	36	46	56	66

information $H = -K \sum p_i \ln_2 p_i$ = INFORMATION THEORY

WHY IS THIS ~~PROBLEM~~ LINK BETWEEN INFORMATION & BIOLOGY?

…GGG GGG…
…GGG AGG…
…GGG GAG…

these three sequences have same probability of occurrence but have v.v.v. diff macrostates

BIOLOGY IS TOO HIERARCHICAL FOR EQUILIBRIUM ORIENTED MEASURES TO WORK

10·8·91
Bio. 215

Prebiotic Evolution

Two main points

① Lots of time available - so rare event could occur

② Or physical & chemical environment such that it was inevitable

Primitive Earth

① Hal Morowitz ... can thermodynamics help out over long period of time?

- how likely is spontaneous assembly of simplest cell?
  - grow up E. coli
  - Calorimeter ... burn them ...
  - output from calorimeter - can calculate ΔH & $T\Delta S$
  - likelihood = $1/10^{10^{11}}$ ~~...~~ ... not even close

∴ need stage by stage progression ... where each stage is somewhat likely

Age of Planet ≅ $4.6 \pm 0.1 \times 10^9$ years
Life Evidence ≅ 3.5×10^9 years
} ∴ max time = 1.1×10^9 years

② Radioisotope dating

ⓐ $N^{14} \xrightarrow{h\nu} C^{14}$ → N^{14} + e^-

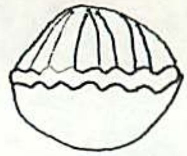
- ½ life ≅ 5600 years
- when one dies no more C^{14} input
- past 6-8 half lives - noise too high

ⓑ ^{40}K → ^{40}Ca + e^-
^{40}K → ^{40}Ar

½ life = 12.4 billion years

- but Argon can escape

∴ should look at multiple decay systems



© $^{87}Rb \xrightarrow{e^-} {}^{87}Sr$ ½ life = 47×10^9 years

EXAMPLE

biotite $^{207/206}Pb \cong 1.7 \times 10^9$

$Rb/Sr \cong 1.65 \times 10^9$

Primitive Earth

Ⓐ ① Earth & Solar System have high concentration of heavy atoms

② So ... probably 2° or 3° system

③ Nearby supernova cause callapse of Solar Systems dust cloud

- exploding stars v. heavy

ENRICHMENT - v. heavy elements could be formed by big star especially at explosion

④ Solar nebulae formed

$$F = G\frac{MM'}{d^2}$$

⑤ Massive entities attract ... bulge in middle gets bigger

⑥ Protosun forms

⑦ 2° centers of condensation w/ enough angular momentum to not fall in.

ENRICHMENT for inside of Solar System ⑧ Sun ignites & light "things" escape & get blown away

ACCRETION Ⓑ ① center of Earth "melts" as accretion incretions

② ∴ Earth can trap lighter elements as Earth cools

- H_2O, H_2, ...

③ CRUST ACCRETION

④ Vaporization of outer surface ≅ 4.4 – 3.9 × 10^9 years

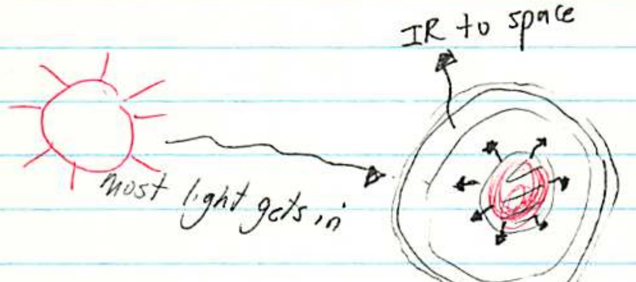
- trying to estimate when last major impacts occurred ... based on impacts (½ life) on Dark Side of moon

Primitive Atmosphere

(a) Prior to 2 bya no free O_2 in atmosphere
(b) Unclear how reducing atmosphere was

Gunnsite churts ··· section through O_2/H_2 interface — -high UrO_2 / -PbS } would only occur w/o free O_2

(c) likely H_2O, CO_2, N_2 & some CH_4, H_2S, NH_3 outgassing



-atmosphere v. turbulent
-high volcanism
-high meteorite impacts
  -wakes create energy

(d) cycles of energy material due to energy flows
  -input = earth + suns heat (IR + UV)
  output = IR 273

(e) order increases w/ input of energy
(f) EXACT INTERACTIONS are v. dependent on T^0
  - $T\Delta S$
  - activation energies (too high T^0 = not stable)
    (too low T^0 = no change)
  -20°C (253K) - 4-500K
    (Urey sugg. this due to low amt of halogens in oceans)

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0.53 – Full O_2 in atmosphere
0.67 – Ediacara → Burgess shale
chordates, arthropods

2.0 – Gunflint - O_2 in atmosphere. Widespread, common biota. **

2.6 – 3.1 } banded iron formations - these precipitated out of oceans - Hayes suggests that there was a variety of competing photosynthetic mechanism *

3.5 – Warrawoona fossils - cyanobacteria & mat (stromatolite) (C[12] higher than in non-biotic fossils of the same age)
- C^{12}/C^{13} indicative of Photosynthesis
3.77 – Issua
- C^{12}/C^{13} indicates higher CO_2

max outgassing of reduced material

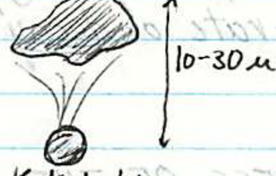
"frustrating impacts" - would have brought in a large amount of reduced organics ***
4.6 – Origin of Earth

Issua - oldest known sedimentary rocks
- contains what some people claim to be microfossils
- C^{13}/C^{12} suggest life

* one mechanism plucks off e^- from ferrous sulfate
- such an organism has been found in Dead Sea

** Gunflint
- ~~mos~~
- no evidence for Eucaryotes

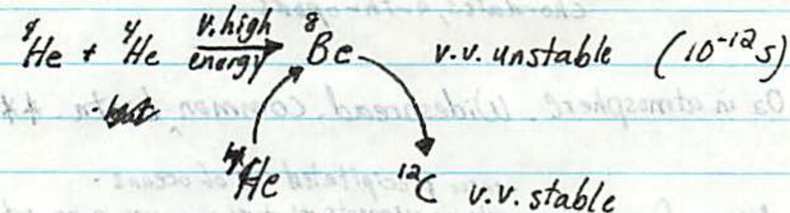
Eosphaera
- maybe precursor to Eucaryote



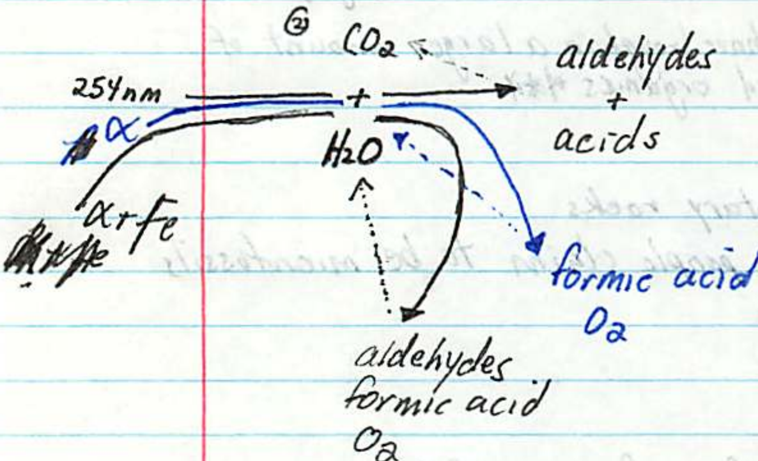
Kakabekia
- also in Buck Creek in Australia
- found to exist currently
likes ~~2%~~ 2-3% oxygen
- and CH_4 ...

*** - Carbonaceous chondrite meteorites
- contains a.a, bases, fatty acids ...
- ∴ may have contributed to "life chemicals"

Examples of Morowitz energy cycles

① 

- this is conversion of enthalpy into entropy decrease
- since the ¹²C is stable, this lasts

② 

Dismutation RXN
- products more reduced & oxidized than precursors

- input of energy leads to decrease entropy (incr. order)
- rate of decay back to CO_2 + H_2O is v.v.v.v. slow

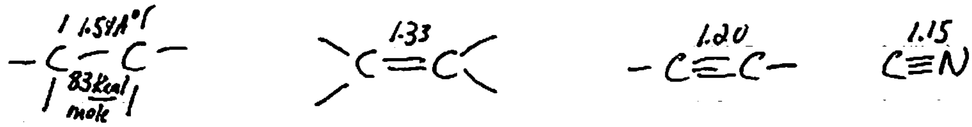
FITNESS OF THE ENVIRONMENT - certain chemicals are more stable than others. ∴ last longer.

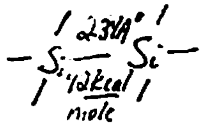
SILICON

C 4 valence e^- chains

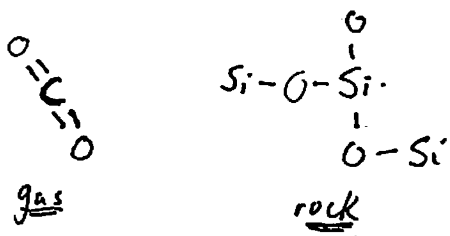
Si 4 valence e^- chains

but



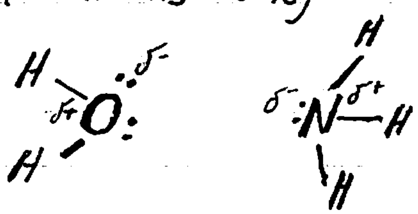


- no double bonds (maybe bec. ~~shell~~ outer shell is too big)



∴ ① w/o double bonds Silicon compounds can't ~~co~~ photosynthesize
② SO_2 not soluble
not gas
∴ hard to move building blocks

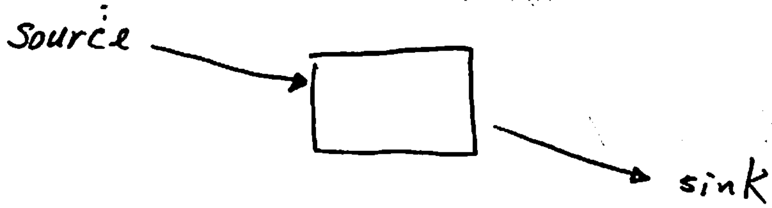
H_2O (would NH_3 work)



-v. mild reagent	aggressive base - v. reactive
-liquid at 100-0°C	liquid at -33 to -78°C
∴ reactions faster	-ice sinks
-ice floats which means freeze from top down.	

∴ self insulating from cooling from above.

Branowski : stratified stability



- If there is a *large* # of microstates and *if* these are randomly distributed,

  and *if* some microstates (rare one) are more stable ...
  then can get *fixed* macrostates.

e.g.

$1 \, {}^{1}H \xrightarrow[\text{energy}]{\text{high}} {}^{4}_{3}He \longrightarrow {}^{12}C$

energy { — kinetically stable; — also kinetically stable

- cannot go directly from H → C
  need intermediates which are stable
  H → He → C

∴ stratified stability: can "climb" up ladder against entropy grade as long as stable intermediates

Life

most common elements in life: H C N O P S
" " " " universe: H He ... not the same

	H	C	N	O	P	S
valence e^-	1	4	3	2	3	2

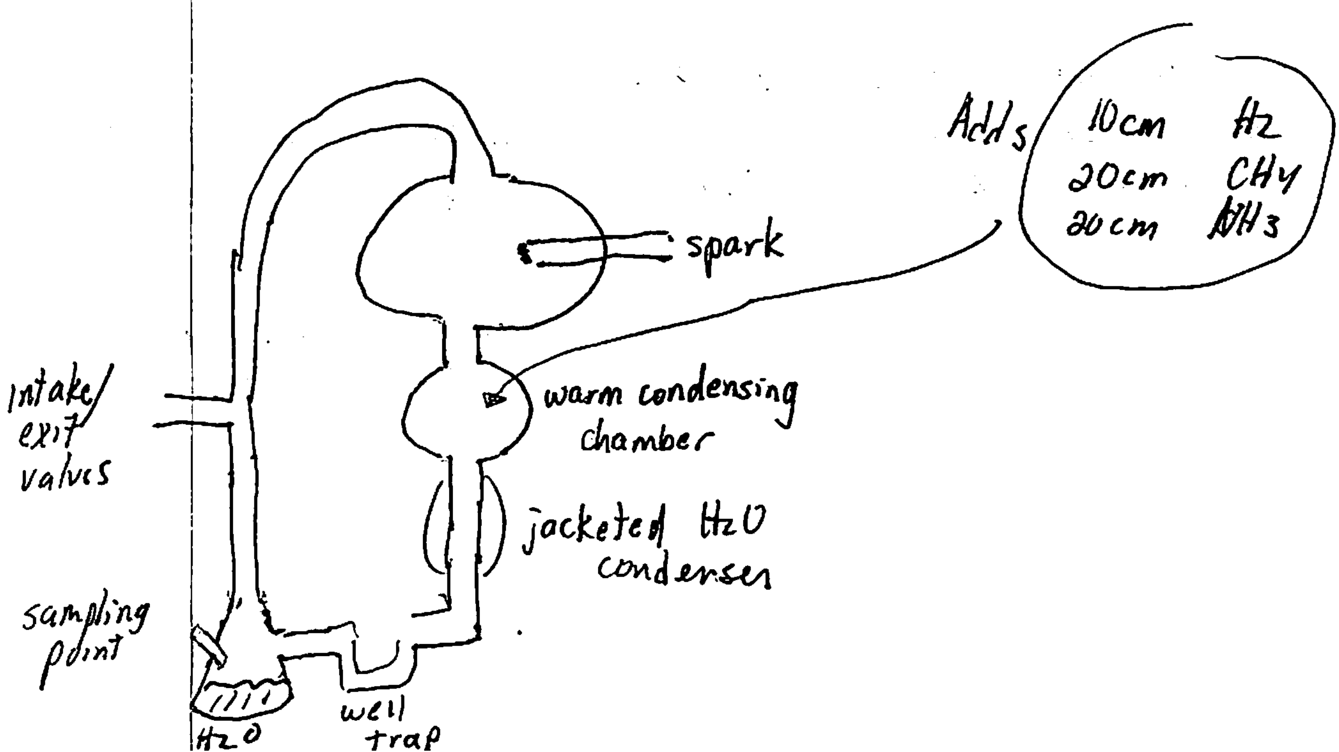
- all form covalent bonds

Original atmosphere

much: H_2O, CO_2, CO, N_2
some: H_2, CH_4, NH_3

Miller & Urey

- Primitive conditions
  1. high electrical activity



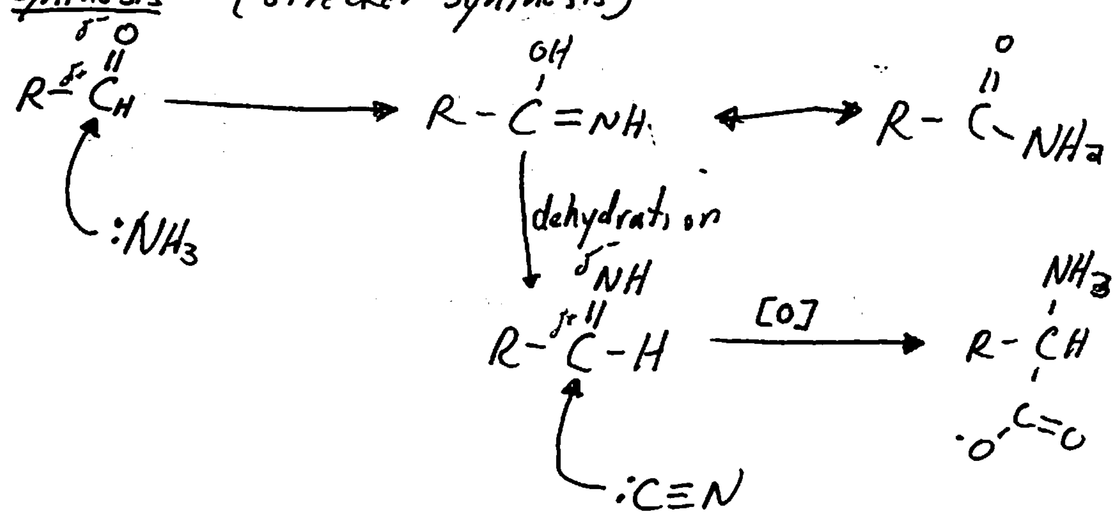
Miller & Urey

① runs system for 1 week

C : 2.1% glycine
1.7% D, L alanine
0.3% sarcosine
α NH_2 butyric ... formic acid ... propionic acid ... aldehydes
cyanide
cyanoacetylene $HC\equiv C-C\equiv N$

start → $C\equiv N$ & $HC\equiv C-C\equiv N$
↓
aldehydes & acids
↓
a.a. . etc.

a.a synthesis (strecker synthesis)



PROBLEMS

① not like primitive earth

- but even if Δ chemicals .. as long as non-oxidizing the ~~conditions are sta~~ results are similar

New Ideas

Abelson suggested that pH of atmosphere was ~ 8-9

$C \equiv N$ in H_2O $\xrightarrow[266]{h\nu\ 240}$ polymerization

↓ decay

a.a.

HCNO

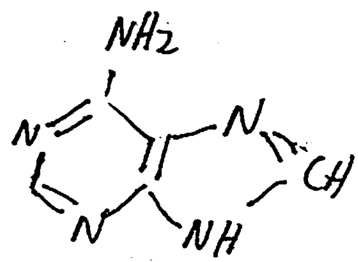
formaldehyde $\xrightarrow{pH\ 8-9}$ C_3-C_7 sugars

ORO & KIMBEL — CYANIDE & CYANOACETYLENE

HCN (1-15M 27-80°C)

↓ let sit

$(HCN)_5$



ADENINE

but 1-15M HCN is unlikely

LESLIE ORGEL · how can we do w/o [high] HCN or lightning

· assumed earth was tilted ∴ seasons ∴ freeze/thaw

① dilute HCN

↓ freeze out H_2O

concentrated HCN

see Sanchez et al JMB 30:223 for mechanism

→ Adenine 30-40% + Guanine

+ many intermediates in contempory synthesis

② cyanoacetylene ⇢ ⇢ ⇢ pyrimidines (much harder)

SUMMARY

HCN ⟶ conc. HCN $\xrightarrow[\text{freeze } H_2O]{pH\,8\text{-}9}$ purines ⟶ a.a.

conc. HCN $\xrightarrow{h\nu}$ polymers $\xrightarrow{H_2O}$ a.a. $\xleftarrow{h\nu}$ CH_4 CO.. NH_3

cyanoacetylene ⟶ ⟶ ⟶ pyrimidines

HCHO $\xrightarrow{pH\,8\text{-}9}$ C_3-C_7 sugars

HC = CH

HC ≡ CH

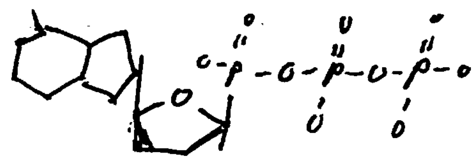
N

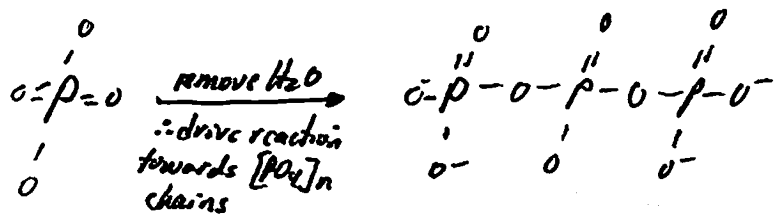
pyrole

⟶ pyrole
↳ tetrapyrole ⟶ heme
chlorophyll

High Energy Compounds

ATP





solution $APO_4 \rightarrow A[PO_4]_2 + H_2O$

polyphosphates can spontaneously react w/ things to form phosphates.

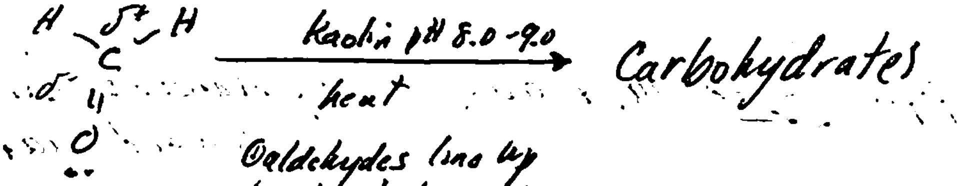
- ∴ wind energy (evaportation) is converted to chem. energy

- many prokaryotes use PP as energy storage

Clays w/ molecular charge separations

e.g. Kaolin in dilute base (pH 8-9) + heat
+ 100M Formaldehyde

Formaldehyde



① aldehydes line up due to electrostatic attraction
② mutual condensation

$ACH_2O \longrightarrow (CH_2O)_x$

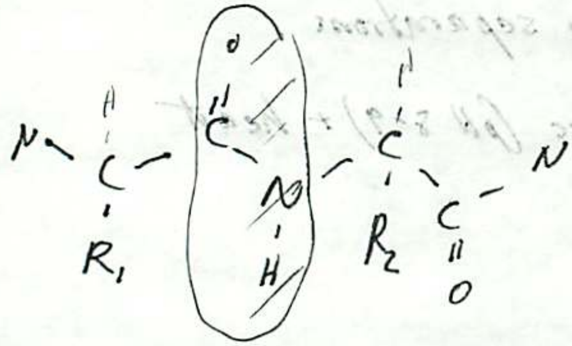
∴ oligomerization could occur in abiotic conditions

Why need macromolecules?
① information storage
② stability
③ compartmentalization
④ consistency

Why from monomers
① historical

How make large macromolecules
① source of monomers → high [ ]
② orientation, proximity → specificity of binding
③ target bond distortion

peptide bond



peptide$_2$ ⇌ $aa_1 + aa_2$ — spontaneous direction is toward $aa_1 + aa_2$

How get the RXN to go in other way
① remove reactants
e.g: Fox's hot rocks
- a zone of a volcanic vent where H_2O is boiling off ... maybe this would help polymerize a.a.

a.a. $\xrightarrow[\text{dry}]{100-200°C}$ 5 - 20KD polymers
ⓐ salt in & out
ⓑ soluble in H_2O } ∴ like proteins
ⓒ UV & IR like proteins
ⓓ mixed α & other linkages

e.g.

$CH_3C(=O)C(=O)OH \xrightarrow[\text{ppt. like thing}]{\text{prim.}} CH_3COOH + CO_2$ — saturation much like enzymes.

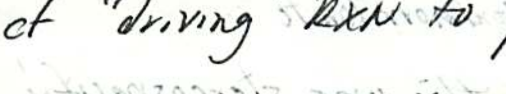
Methods of "driving" RXN to polymerization

① a.a + a.a. ⟶ prot + (H_2O) ⟶ remove

② orient molecules
- clays have ⓐ v. large SA
  ⓑ large charge separation potential

- Kaolinite: $Al_4(OH)_8Si_4O_{10}$ ...

Montmorillonite: Al, Mg · OH · Si_4O_{10} · Na_2, Ca H_2O, ...



see Degons + Matheja

Multiple levels of repeating, finely divided structures with charge separation.

Degons & Matheja — Montmorillonite — #1 pep

	80°C 7 days Montmorill free	80°C 7 days Montmorill polym	80°C 7 days Kaolinite free	80°C 7 days Kaolinite polym
Asp	93.7	3.3	3.1	96.9
Ser	86.9	—	98	1.6
Glu	3.6	934	1.2	98.7
Pro	101	—	103	—
Gly	99.6	3.8	99.4	0.6
Ala	99.1	2.1	89.3	15.0
Val		—		—
Phe		1.3		1.0
Lys	#1 peptide =		#1 peptide	
His	$Glu_{100} \cdot Asp_4 \cdot Gly_4 \cdot Ala_2 Phe_1$		$Glu_{100} \cdot Asp_{100} \cdot Gly_1 Ala_{16} Phe_1$	

If add urea to montmorillonite + a.a. precursors you got

$$\text{a.a. precursors} \xrightarrow[\text{Montmorrilonite}]{\text{urea, }80^{\circ}C} \text{a.a.} \longrightarrow \text{proteins}$$

- possible that this was stereospecific

STEREOSPECIFICITY

① needed so that macromolecules have specific structure
α helix ... held together by H bonds

② α helix containing proteins are more stable
∴ chemical selection

③ why L vs D.

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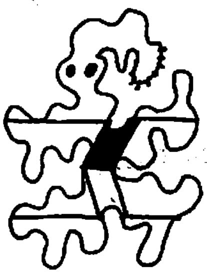
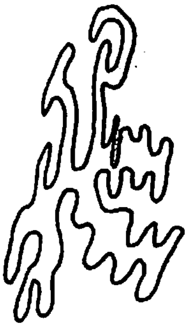




Stereochemistry

① How do macromolecules become stereospecific? - stability
② Why D sugars and L amino acids?
- ⓐ Prevailing light polarization leading to differential formation/destruction
- ⓑ Differential decay
- ⓒ Stereospecific adsorption see Bondy & Harrington
- ⓓ Biological racemization
  [redacted]
  - organisms can convert L-to-R

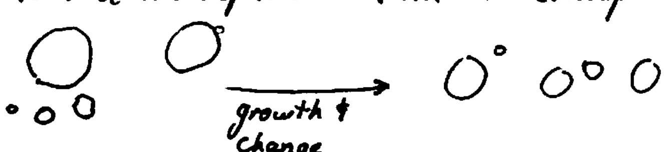
Prokaryotes
- haploid simple circle
- predominantly clonal reproduction
- Periodic Selection
  - in chemostat one clone takes over ... thus "neutral" genes may be fixed because they are on the clone
  - analagous to hitchiking

ⓔ Periodic selection -- an L specialist gets 1st big advantage. like Simpson adaptive zone -- if you're first then you're best

Like in Math
① prove possibility
② then work on uniqueness

Polymerization
① Pre-proteins
② Pre-nucleosides

Self partitioning
① Current Proteobacteria membranes are only 25% lipid
② Proteanoid microspheres -- from Fox's studies



- like crystalization

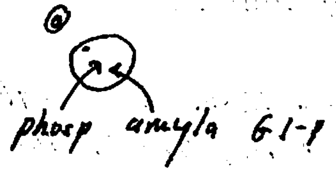
Self-partitioning, cont.

- Coacervate formation
  - almost any macromolecules with polarity in H_2O can spontaneously form partitioned bodies.

- Oparin
  - can make stable coacervates from RNA & lysine; from many things
  - " " " " " gum arabic & albumin

ⓐ took gum arabic/albumin coacervates
ⓑ added purified enzymes & got taken up
phosphorylase + G-1-P + amylase

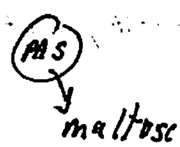
ⓐ



ⓑ

$G1P \xrightarrow{P} starch$

ⓒ



$S \xrightarrow{A} maltose$

ⓓ incr. in size

Chemicals $\xrightarrow{energy}$ polymers → catalysis

polymers → light absorption molecules

polymers → coacervates

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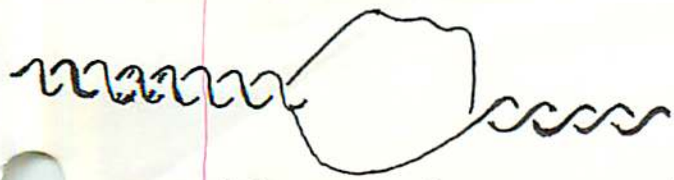

Information Transmission & Coupling to Energy needed for transmission

See Quasler -- the emergence of biological organization

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Biochemical Evolution

How does information storage and "function" become linked?

Why are proteins good catalysts?

① shape, stereospecificity - flexible and stable

② diverse properties of 20 aa.
- polarity
- charge
- shape
- diversity of potential catalytic groups

③ switch catalytic properties on/off

Why not good for information?

① once information is there its hard to get out

② there are no forced symmetries.

Why nucleic acids good?

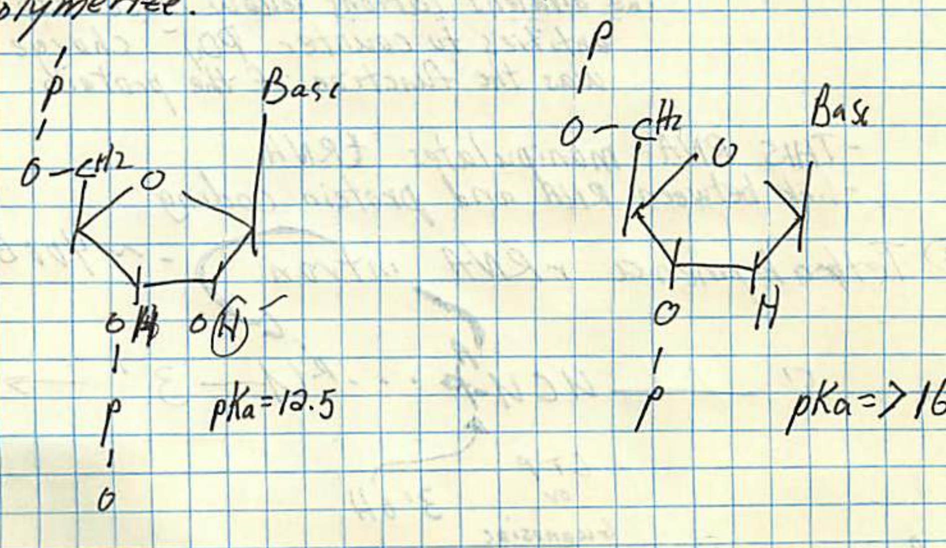
① self-complementary ...AU... / ...UA...

② more H bonds possible

· H bond $\Delta G = -1$ kcal/mole

∴ small oligomers in solution will "favor" by energy... the associations of their compliments. ∴ all you need is the ability to polymerize.

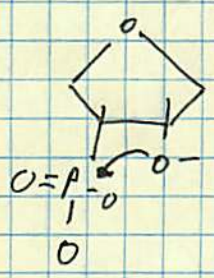
NB. DNA vs RNA
① OH group



RNA vs DNA

pKa < pKa

∴ RNA has more O^- ion



→ - self cyclizing
- chain degradation

-DNA is most likely post-biotic

NB - Attenuation

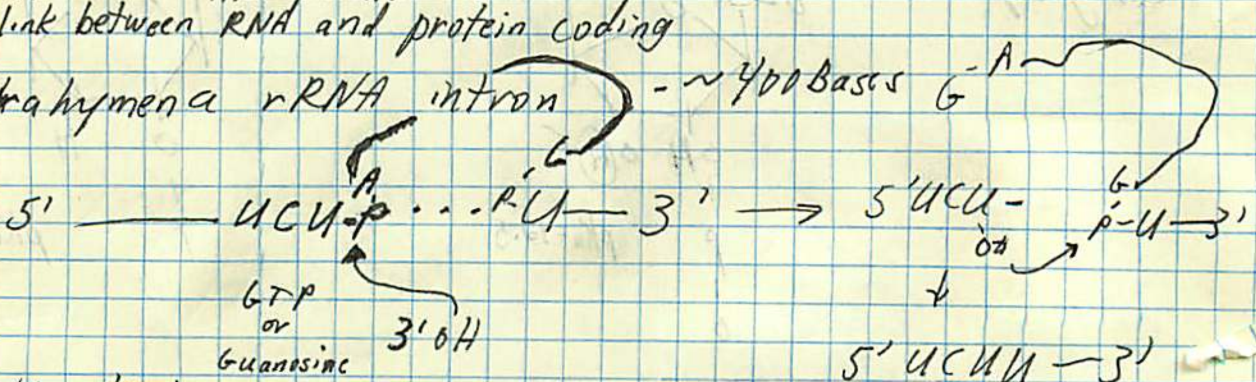
- RNA was folding up into alternative conformations

RNA Catalysis

① RNAse P - S. Altman
- v. hard to purify as "a protein"
- couldn't remove "RNA" [redacted] contamination."
- when they did... protein lost catalytic activity
↳ then RNA was shown to be catalytic part in the presence of high Mg^{++}
- the divalent cations allow close association of RNA entities to counter PO_4^- charge repulsion. This was the function of the protein.

- THIS RNA manipulates tRNA
- link between RNA and protein coding

② Tetrahymena rRNA intron - ~400 Bases



Resembles tRNA

③ telomeres synthesis, involves catalytic RNA

The RNA world

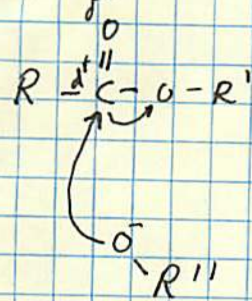
- RNA catalyst
- RNA stablized by 2° structure

NB -- many cases of symmetries & palindromes involved in control regions.

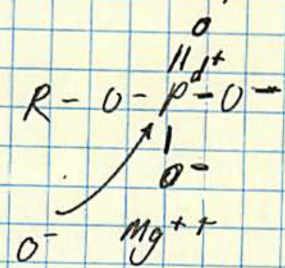
Problems

① information assignment
② alignment of a.a.
③ compartmentalization - clays or coaccervats
④ peptide bond formation

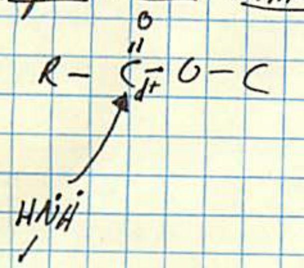
Nucleophilic ~~transesterase~~ estorification is v. similar to peptide bond formation.



RNA catalyst



Peptide bond formation



-what catalyzes this bond...
seems to be a property of the rRNA itself.

How does the information system originate?

see
② Goldberg + Wills
① Crick
④ L. Orgel
③ Weber & Lacy
⑤ Junk

Problems with information system:

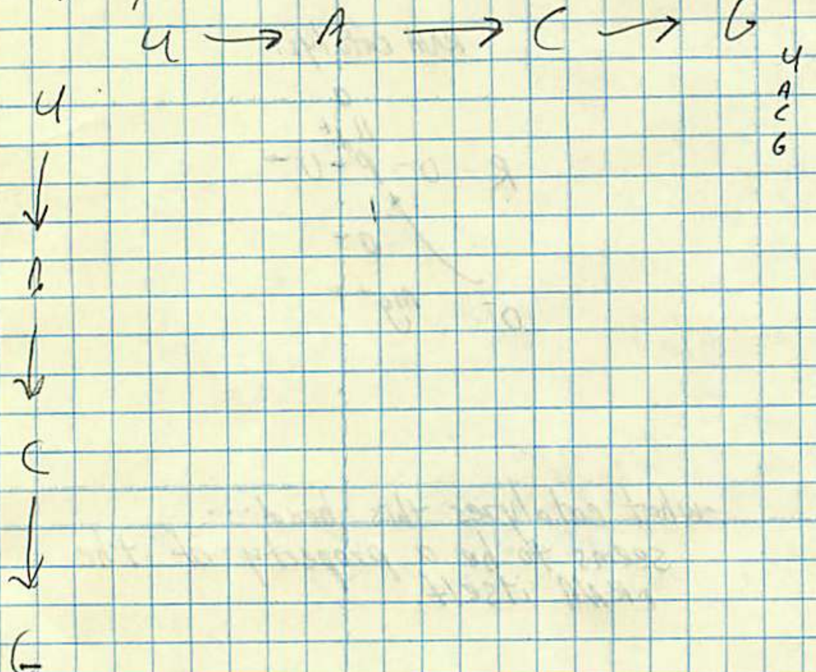
(1) Why is the code universal?
  - only exceptions in organelles (apparently post-biotic)

  (a) <u>hitchhiking</u>?

(2) If code is universal why are some potentially non-pre-biotic a.a. part of code?

(3) How specify 3 nucleotides at a time?

How specify code?



(1) degeneracy grouped

(2) 3rd position most degenerate

(3) those with "two" codes → always
  XY purine
  XY pyrimidine

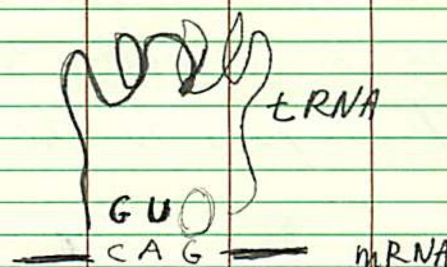
(4) those with 4 codes
  XYN = one block

(5) <u>But</u> don't look at information of storage unit but of message unit.

Origin of a.a. Codons

	U	C	G	A	
U y c	Phe	Ser	Cys	Tyr	U
	"	"	"	"	C
	Leu *?	"	Trp	STOP	G
	" *?	"	Trp/STOP	"	A
C	" *?	Pro ?	Arg	His	U
	" *?	" ?	"	"	C
	" *?	" ?	"	Gln	G
	" *?	" ?	"	"	A
G	Val *	ala	Gly *	Asp *	U
	" *	"	" *	" *	C
	" *	"	" *	Glu *	G
	" *	"	" *	" *	A
A	Ileu *	Thr ?	Ser *	Asn	U
	" *	" ?	" *	"	C
	" *	" ?	Arg	Lys	G
	Met	" ?	"	"	A

DNA	AGCT
mRNA	UCGA
tRNA	AGCU



① the third position can "wobble" so don't need as many tRNAs as codons

Crick - argued that the code was a frozen accident. Once code was partially established the only ones that could invade would have to be similar

Goldberg & Wilts - suggest that this minimizes effects of mutations.

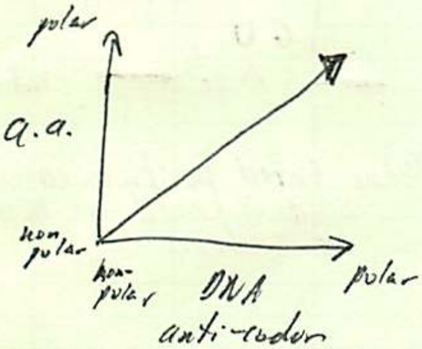
ⓐ non-polar all together
ⓑ polar all together

∴ changes in 3rd position has no effect in fourfold degenerate and transitions at 3rd have no effect on twofold degenerates.

CANNOT DO ANY BETTER

- If you examine the codons according to what the bases are in DNA or tRNA.
- Polarity of DNA bases A < G < C < T

If you take the first two nucleotides of the DNA part of the codon and arrange these 16 according to hydrophobicity/philicity and compare to the a.a. the code for.



This may be a footprint or relic of coacervatrons.

Questions

① Can you bias the formation of small peptides by adding oligonucleotides?

Lacy-unpublished - Yes -- thus in open solution anticodons may associate with their a.a.

② Is it possible to bend tRNAs so that they would work w/ 2 bases? - may be that 2 bases is too small to get efficient bend, so that multiple tRNAs can fit.

③ why 1st two not last twos?

J. Wong

- continued on ideas of Crick about "invasion" of code.

① Identified GROUP I a.a. which he considers pre-biotic (see * on Chart)

- notes - many post translational modification occurs in current systems
- maybe - current a.a. synthesis systems are relics of post-translational modifications in past.

— THUS STRUCTURALLY RELATED A.A. WOULD BE GROUPED.

- selected bacteria to replace Trp w/ 4-Fluoro-Tryptophan to see if "invasion" could occur.

Molecular Fossils

① JCWShephard

- suggests that there is evidence

RNY mRNA } statistical bias for codons
YNR DNA } of this form.

U. Texas ② Bock et al: suggestion that in contemporary tRNA & rRNA sequences have substrings on 9, 11, ... nucleotides

Assumption that 1st protobionts were heterotrophic.
1st protobiont may have been ~~chemo~~ photosynthetic.

hv → double bond → decay (if hv low energy)
double bond → fluorescent
double bond → reacts

Thus light could lead to proton gradients which are currently present in all energy generation

11-05-91
Bio 215

Evolution of Metabolic Systems

see Horowitz Evolving Genes & Proteins
Eigen & Schuster
Hochachka & Somero
Watt Am Nat 127:629

HETEROTROPHY AUTOTROPHY → ORIGINS

MOL. & POP. GENETICS → PIECES OF MACHINE

ARCHITECTURE ⟷ PIECES OF MACHINE
(adaptation, constraint)

ORIGINS, ARCHITECTURE → EVOL'N OF METABOLIC SYSTEMS

Horowitz ('65)
- proposed notion that metabolic pathways evolved backwards
- e.g.

(A)(A)(A)(A)(A)
① Adenine in primitive soup
② use it all up

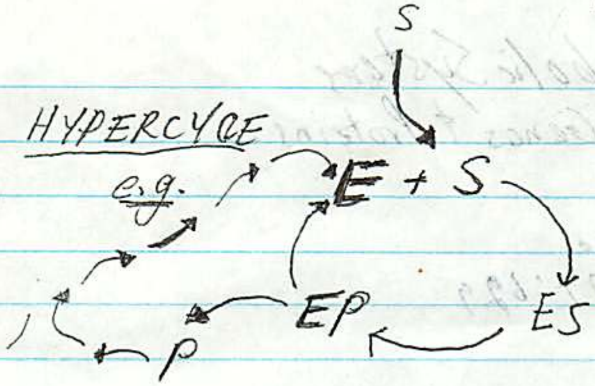
(B) → (A)
③ those that "advance" will be able to make adenine from something else

- if this is how metabolism originated then there has been a lot of condensing of RXNs & pathways.
~~because~~

Eigen & Schuster ('77 & '78) Springer-Verlag
- HYPERCYCLE
① more stable molecules would be more common in "soup"
② if a cycle makes part of "ITSELF" it will increase in representation in soup.

Where are relics?

HYPERCYCLE



Pre-Darwinian selection

- this cycle can then be hooked to others
- if P or E can stabilize other cycles then these cycles will co-stabilize

HOTPOTATO

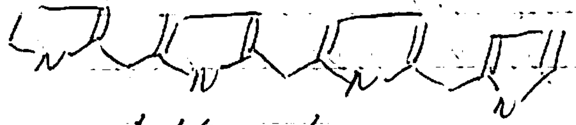
- will pick up blue/green light
- e^- gets excited → leads to 3 possibilities
    - ① decays into translations/rotations of surrounding bonds (e.g.: melanin)
    - ② fluoresce out (usu. at longer wavelengths)
    - ③ chemical RXN (more likely w/ lower λ of hν.)

∴ ANY photochemical that generates a high energy electron will be stabilized if it can pass of the e^- to another molecule.

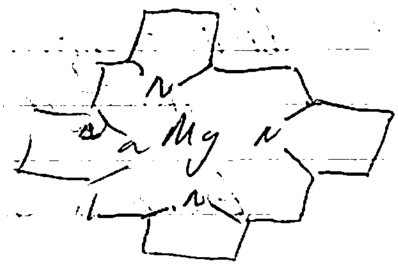
Stoeckinius et al BBA 505:217

How do you test these theories?

① examine diversity of Photosynthesis



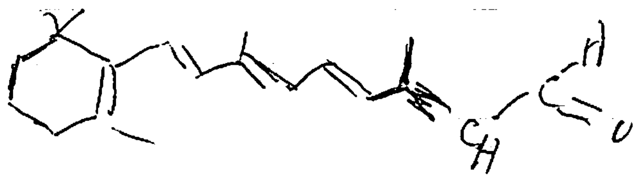
light antennae



capture

- but also have Carotenoids

- Halobacterium - facultative photosynthesis



trans-retinol

- bound to small protein (bacteriopsin) through aldehyde via Schiff's base

(retinol) $R_1\overset{H}{C}=O + H_2N-R_2$ (opsin)

$h\nu \longrightarrow R_1\overset{H}{C}=\underset{H}{N}-R_2 \longrightarrow R_1\overset{H}{C}=N-R_2$

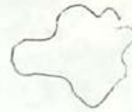
H^+

- proton pump
- makes ATP

- THIS IS

① simple photosynthetic machinery

② membrane is mostly protein



Innovations
- how do you change roots of systems
- how do you change quantitative processing

Hochachka & Somero

Understanding Metabolic Architecture
must include reproductive success of system.

Enormous diversity of metabolic systems.

11-07-91
Bioch. Evol.

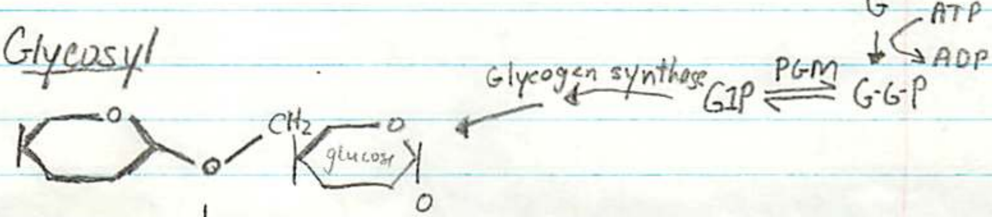
Force balances can limit flow:

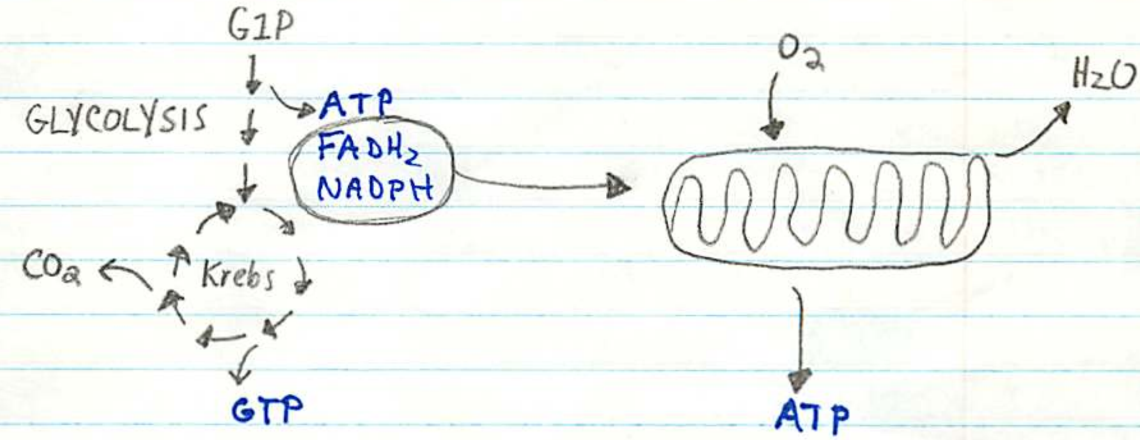
efficiency $= \eta = \dfrac{-J_o X_o}{J_I X_I}$: [redacted]

$\therefore J_o$ is $\dfrac{J_I X_I \eta}{X_o} = J_I \eta \cdot \dfrac{X_I}{X_o}$ (Boundary Condition)

Evolution of alternate pathways
① why choose another
- can use carbohydrate metabolism

Glycosyl





$$\underset{686\ kcal/mol}{\text{glucose}} \longrightarrow CO_2 + H_2O + \underset{12.2\ kcal/mol}{36ATP}$$

$$\frac{12.2 \cdot 36 \hat{=} 4400}{686} \approx 67\% = \text{v.v. high yield}$$

But rate can be very high in non-equilibrium

Alternatives to glycolysis

① Fermentation

ⓐ no O_2 present - ∴ mitochondria can't oxidate NADH

ⓑ much less efficient 2 vs. 36 ATP
- but if carbos are limiting then O_2 doesn't disappear.

② Lactate [redacted] shunt

ⓐ pyruvate
ⓑ NADH recycled immediately in production of lactic acid with LDH!

ⓒ but Heart & Brain never go anoxic
- different Km for LDH than muscle LDH
- soak up lactate from blood & get rest of ATP's

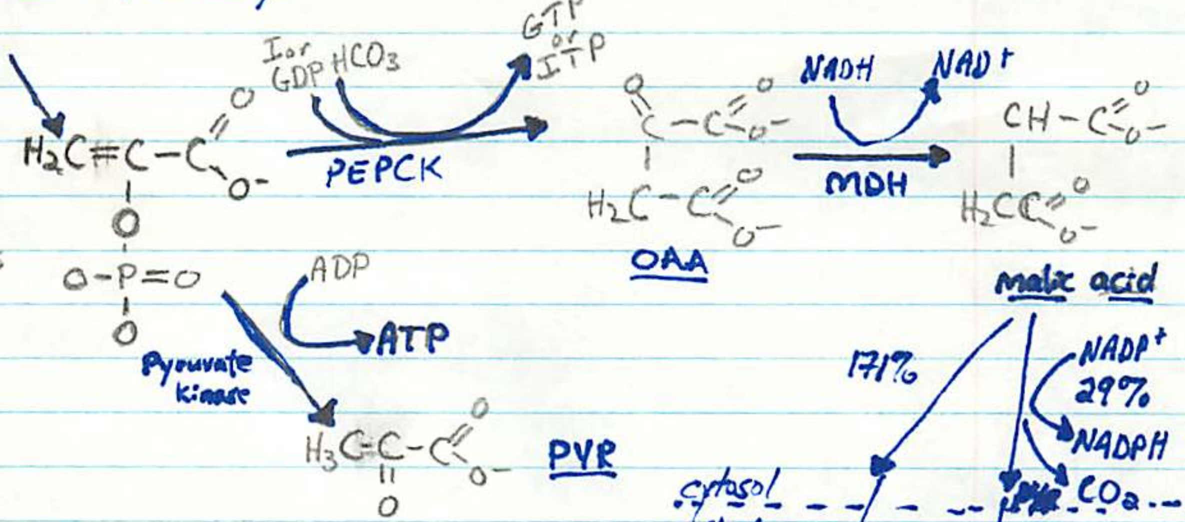
③ Chronic anoxia organisms

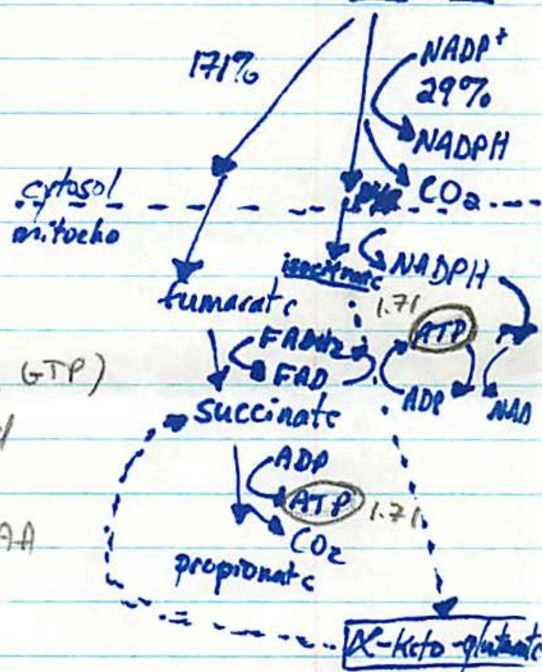
- e.g. - bivalves which shut up to avoid sun
  - less O_2 ⟹ decr. metabolism

- send pyruvate into alternative pathways

Alternative pathways - info about evolution of complex machinery

PEP
- phosphate stabilizes this





① PEPCK ···> OAA ···> malic acid
- yield is about the same (ATP vs GTP)
- but C-4 not C-3 compound

Glu ⟶ 2GTP + $2NAD^+$ + 2OAA

vs

Glu ⟶ 2ATP + 2PYR

- prob

- cytosolic & mitochondrial MDH's

∴ 6.42 ATP/glucose instead of 3

- **α-Keto-glutarate**: takeoff point for many synthesis

- to link up Kreb's cycle all you need to do is to link α-keto to succinate w/ acetyl.co.A

Why two?

① suggested that (by Vogel)

④ original - no Lysine (group I)

↓

- this does not match phylogeny

DAP (group II) → no lysine (group III)

↓

AAA

② Norm Weeden (in Clarkia)

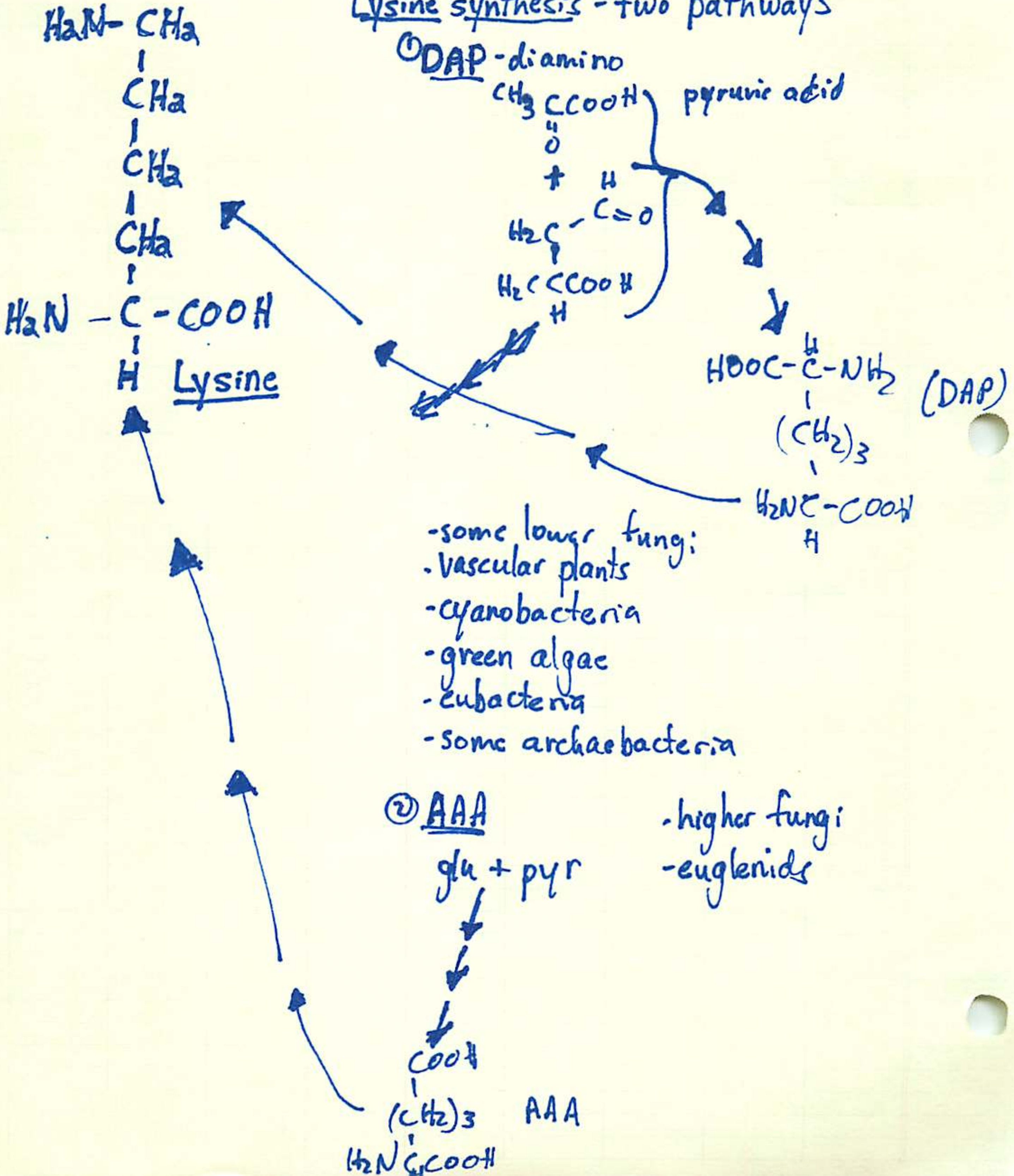
- separate isozyme in nucleus & chloroplast
- plastid isozymes were more similar to each other and to prokaryotes than to those of the cytosol.
- plastids ran their own glycolysis
- the CYTOSOL was f(x)ally an animal
- euglenids ....

Thus this makes lysine synthesis match phylogeny.

Metabolic Network Theory

-note: choice of metabolic pathway is ~~dep~~ dependent of thermodynamic parameters which can be played with

Lysine synthesis - two pathways

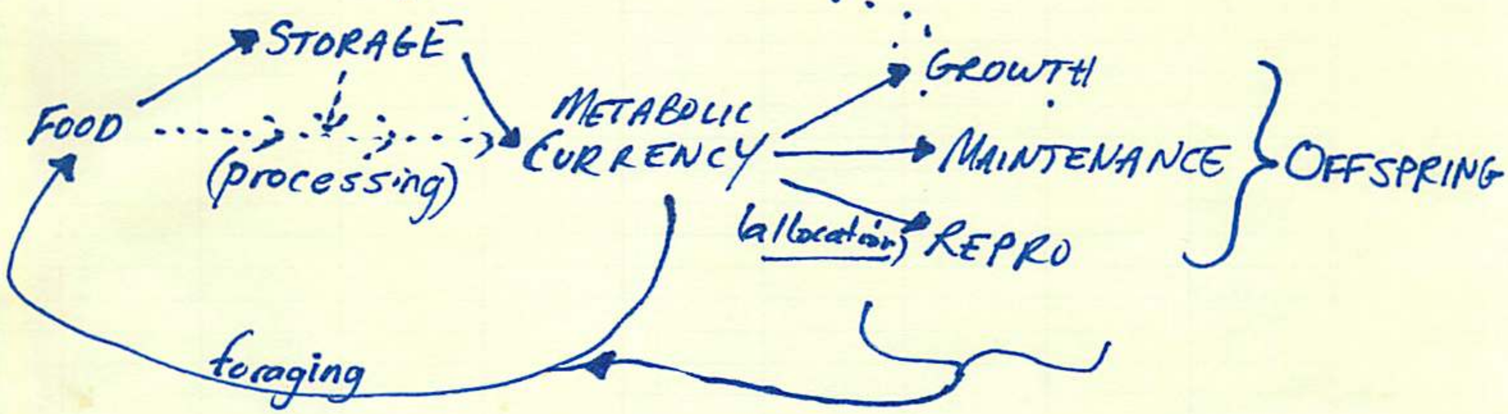


-some lower fungi
-vascular plants
-cyanobacteria
-green algae
-eubacteria
-some archaebacteria

② AAA
-higher fungi
-euglenids

Bio 215
11-6-91

Metabolic Organization



- Separation of processing & allocation allows better connection of adaptation to fitness.
- but until Watt '86 this was not expressed explicitly in terms of applying adaptive differences to fitness.

Adaptation → Fitness (Indeces of fitness)
ⓑ
Characters "VISIBLE" to selection
ⓒ

$K_{eq} = e^{-(\Delta G/RT)}$

Efficiency = output/input = $n_0 \Delta G_0 / \Delta G_I$

ΔG_I = free energy in input compound
ΔG_0 = same for output

- but in equilibrium models cannot get a measure of power because no rate.
- can use % completion of RXN as correlate of power

% completion = $\frac{K_{eq}}{K_{eq}+1}$

THERE IS A MAX YIELD

Biochemical Evolution

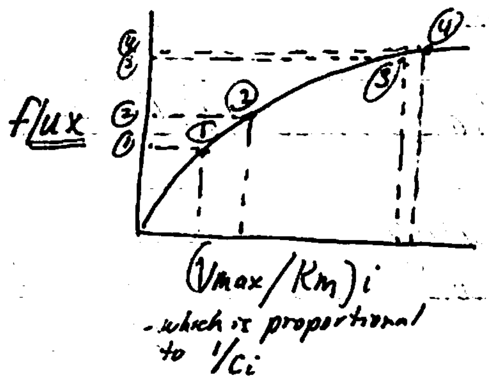
Hartl & Dykhuisen 1985

- steady state metabolism (rates constant, concentrations constant)

Transient conditions - have to try to get response time down to zero

- $\Sigma C_i = 1.0$ (normalized)
- suppose $\Sigma C_{PFK} = 0.87$ then all others have small contribution.

Thus the power of selection on the other steps is greatly diminished.



- if natural selection favors flux then 2 will be favored over 1.
- but 3 vs 4 not much different

Thus as evolution improves a system over time, genetic variability will be primarily neutral.

Problems

(1) assumes an incredibly stable environment

(2) assumes

(a) no heterozygote advantage (OK for haploids)

(b) no dominance effects

(c) directional selection

How do you evaluate performance? see Watt '85 Am Nat 125:118-43

① Bioenergetics
- won't always apply
  - ⓐ state variable regulation
  - ⓑ metabolic processing
  - ⓒ " " allocation

Mytilus - Lucine amino peptidase (R. Kochna)
- role in osmoregulation
- diff. alleles change environments in which all other enzymes function

Tigriopus - copepod transaminase (R. Burton)

Funduluς - Lactate dehydrogenase

N → S
0° → 30°C (1°C / ° Latitude)

pyruvic $\xrightarrow{LDH}$ lactic
NADH → NAD⁺

LDH-A (muscle) ⟶ lactate
LDH-B (heart) pyruvate

- also has allelic isozymes (isozymes) at LDH-B
  B^b, B^a

LDH continued

(1) Tetramer - 5 possible subunit conformations in heterozygote

4a, 3a:1b, 2:2, 1a:3b, 4b

/ / /// // /

		bb	ab	aa
kcat/Km	10°C	5460 ⟷	4860	2540
"	25°C	6230	6030	5480
"	40°C	5020	6460 ⟷	6530

-Km does not change linearly with T°. ∴ as T° decreases, the Kcat/Km may go up because ΔKm isn't linear.

(2) the heterozygote is closer to the favored genotype at both ranges.

-but ~~don't know much~~ what about the ecology

(3) Does this metabolic system have an organismal level function that could explain polymorphism.

(a) blood cells

-fish use ATP (not DPG) to shift Hb curve

-with higher V_{max}/K_m ... higher ATP levels can be maintained

this effects →

(b) swimming speed

(c) egg hatch rate

Note

(1) multiple genes

(2) multiple alleles

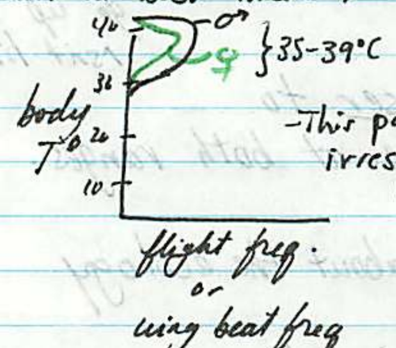
(3) regulatory differences in enzyme levels $[E]_N = 2[E]_S$

-THUS structural difference may not be enough

WATT et al - COLIAS glycolytic enzymes

① easy to work on
② highly phenotypically variable

Ⓐ Behavioral thermoregulation (many orders)
① burning flight muscle ATP by shivering (working flight muscles against each other)
② can at best incr. T° 4-5°C above ambient



-This pattern is same for all Colias irrespective of air T°

ⓐ basking -- 

- behavioral — ① change absorption (insolation)
- genetic/developmental ② change thorax insulation

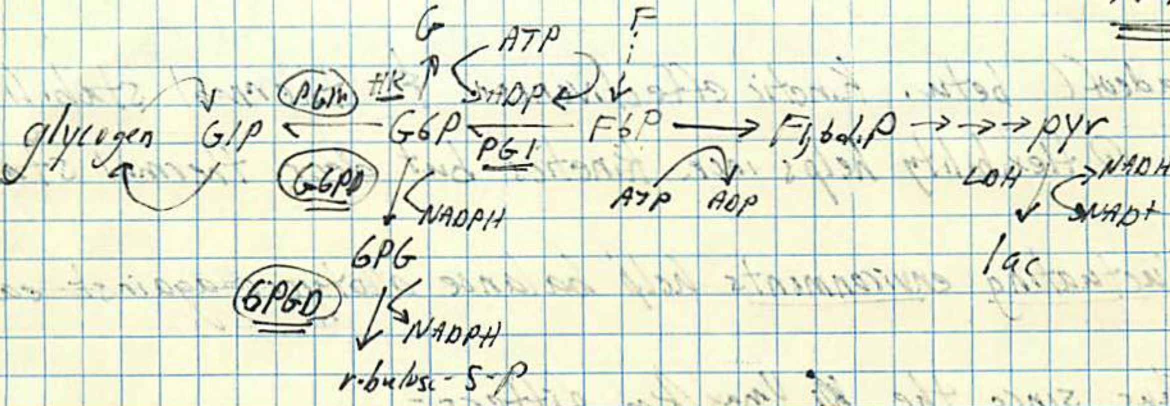
} polygenic so natural selection can fine tune.

-- This filter still has problems
- high altitude, high wind, low T°
- too dark ⟶ occasional cooking
- too light ⟶ too cold

FILTER CANNOT ISOLATE FROM ENVIRONMENTAL EXTREMES

ALL FITNESS DEPENDS ON FLIGHT.

11·19·91



Natural Variation in Wild

- PGI, PGM, G6PD -- ~~all~~ popula both C. eurytheme & eriphele have 3+ alleles of each

- optimum T° = 35-39°C

-

To minimize effect of non-control steps on ability of control steps ~~to respond~~ to work transiently.

Vmax/Km = high in non-control steps

- Asymmetric heterozygote advantage

23% 55% 72% 83% 90% 36% (% of activity maintained after thermal stress)

Tradeoff betw. kinetic effectiveness & thermal stability
① flexibility helps incr. kinetics but decr. thermal stability

Fluctuating environments help balance allotypes against each other.

Thus since the ~~Ki~~ V_{max}/K_m differs -
- should be able to observe flight differences of diff genotypes
$3/4 > 3/3 \geq 4/4$

1980 - heat spell allowed natural test - more stable

- K_m is more variable part of V_{max}/K_m

- So ... what are results
① diff V_{max}/K_m
② diff thermal stability
③ diff flight patterns in wild that fits ① & ②
④ diff heat response " " " " " "
⑤ diff ♂ mating success (better flight = longer search + better courtship)
⑥ no detectible larval selection
- newly eclosed individuals are at Hardy-Weinberg

⑦ no differential expression

⑧ diff fecundity

⑨ diff survivorship

So what does this mean?

① **no** "attempt" to incr. enzyme level

② no optimal homozygote has been produced

③ MANY CONSTRAINTS

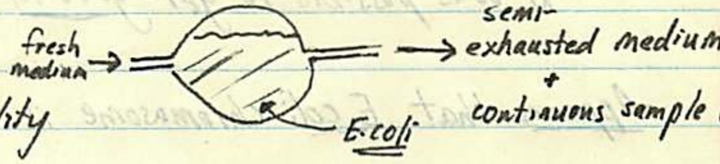
- Pentose shunt doesn't run in flight muscles
- PGM doesnt run

- male mating success differences in PGM & G6PD may be due **to** pre-adult developed differences in nutrient reserves.

Biochemical Genetics

What is visible to selection?
① functional diff. must be high
② role in process must be important
③ role of process in energy (or N, or C) budget on state variables

Hartl and Dykhuisen



\+ continuous sample of population

① E.coli has enzyme variability
② Haploid
③ PGI appears neutral
④ 6PGD
- two main alleles have relatively diff. Km's
- when gluconic acid was sole carbon source there was no selection difference
- but found gluc. acid dehydrogenase so wasn't simply fueling this step

G6P ↓ 6PG ← gluconic acid ↓ ribulose-5P

⑤ Knocked out gluc. acid dehydrogenase and major directional selection for kinetically favored allele.

Thus 6PGD alleles are neutral in some conditions and selective in others. This fit in with Wright's shifting balance

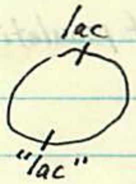
Thus when role of enzyme becomes central to energy budget -- it is more visible to selection.

Phylogenetics
① Why hasn't optimal allele arisen?
② If heterozygotes are best, why aren't genes doubled?

How do new gene functions originate?

Barry Hall - see evolution on a petri-dish

- Evolution of new gene functions
- LacZ - β-galactosidase
  ① persistant reports that lacZ⁻ bacteria on lac-minimal medium it was possible to get growth. [redacted]



- Appears that E. coli chromosome is relic of duplication

— CRYPTIC lac operon 180° away from normal E. coli

lacZ⁻ deletion

↓ selection

34 "lac"+ (31 inducible ; 3 constitutive)

- functions
  - normal lacZ : splits lactose, lactalose, lactobionate, galactose-arabinoside
  - "lacZ" I, "lacZ" II

	normal lacZ	"lacZ" I	"lacZ" II	III	IV
lactose	+	+	+ (slow)	+	+
lactalose	+	−	+	+	+
lactobionate	+	−	−	−	+
gal-arab	+	+/−	+/−	+/−	+/−

Thus - "lacZ" have been reverted from

group selected not on lactose but lactalose

> Can only get lactobionate + by 1st selecting on lactose (I) then lactalose (III) then lactobionate.

- Thus past history is crucial in determining future evolutionary prospects are ; and equally crucial is order of environment.

- Suggested that it was a problem of multiple simultaneous mutations.

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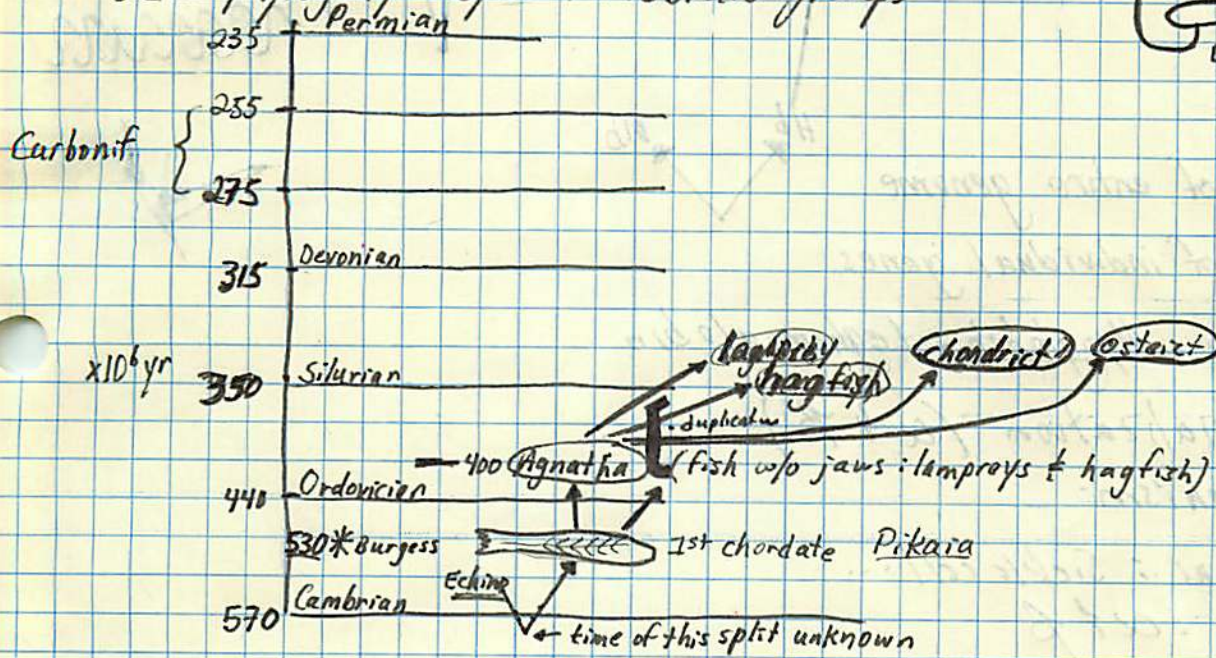
11·26·91

Barry Hall contd

- Role of cryptic genes in Microbial Evolution (MBE 1:)
  1. Rare E.coli could use anomalous Carbon sourses
  2. Concluded that cryptic genes are less prone to mutations than pseudogenes
     - modeled this in terms of rare exposure to substrate.

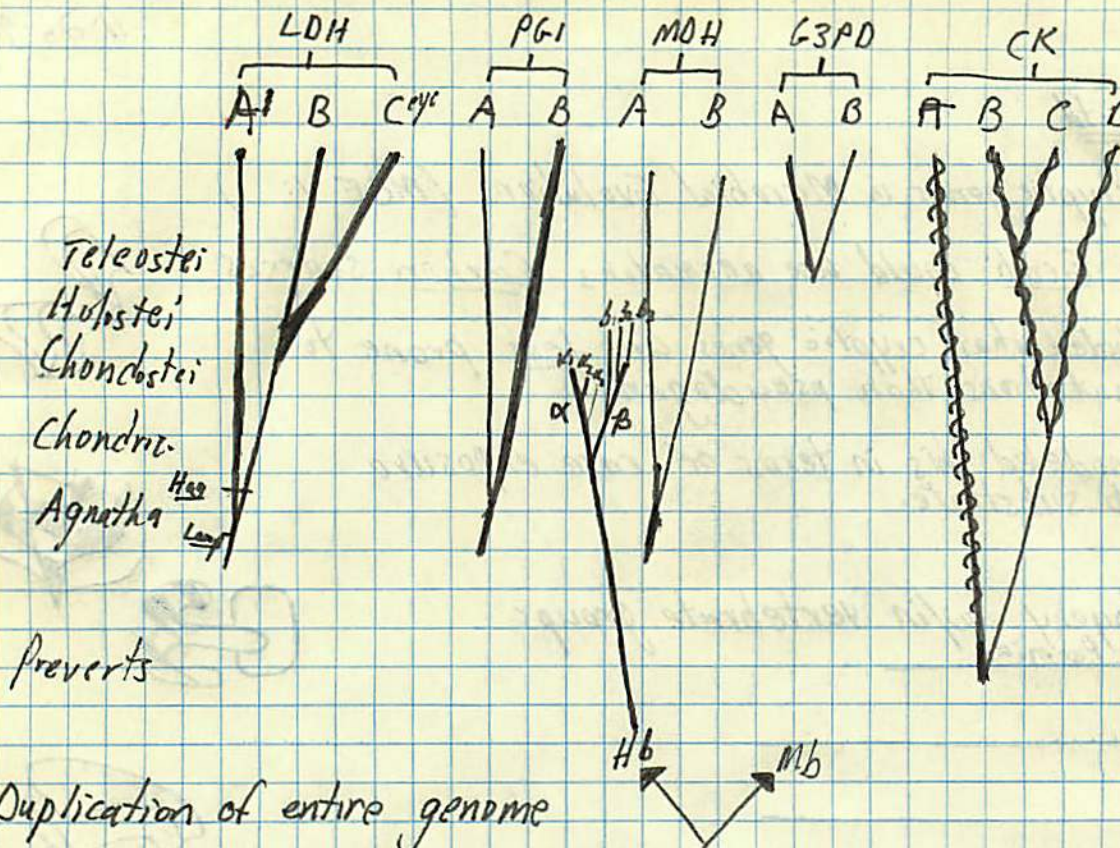
Gene phylogeny w/in vertebrate groups



- Lampreys have 1 LDH A that is like muscle type
  Echinos " " A " " " "
  Tunicate " " A " " " "

- Hagfish have 2 but B gene is like A.

Conclusion
- appears to be a duplication of the entire vertebrate genome in the past

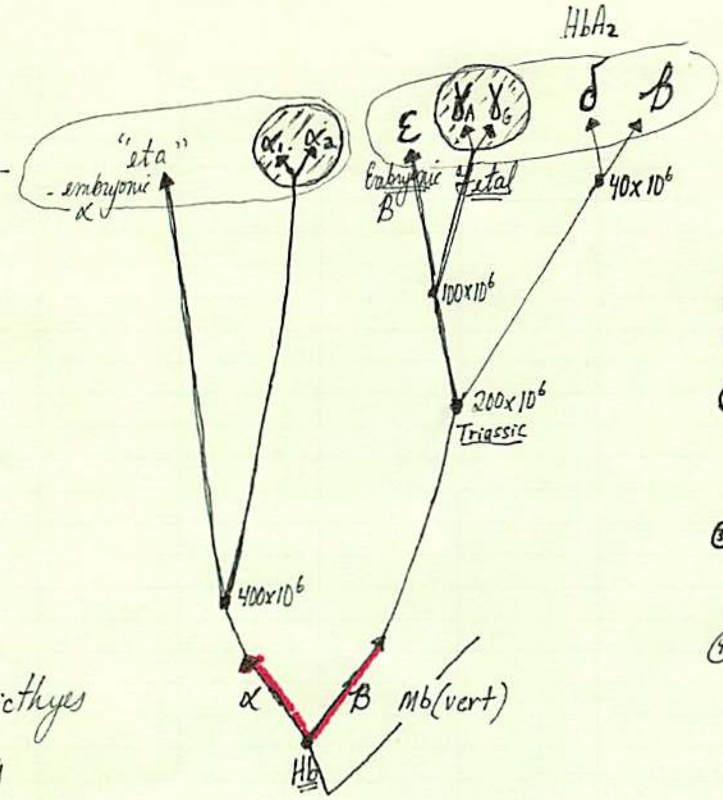


Duplication of entire genome

Duplication of individual genes

- <u>Hemoglobin</u>, <u>Myoglobin</u>, Leghemoglobin
- gene specialization (α + β)
- polymorphism
    - humans : Sickle cell...
    - mice : α + β

Phylogenies of hemoglobins



Inverts Hb analogs

1. 16 KD monomers/oligomers : e.g. insects (midges), molluscs
2. 30+ KD "monomers" : crustaceans
   aggregate ⇒ 800 KD
   (2 Domains)
3. multidomain hemes — crustaceans, molluscs
   (8-20 in linear polymer)
4. 16 KD monomers/oligomers
   (only some have heme)

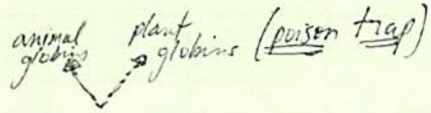
Chondrichthyes

Agnatha

Preverts

Prostomiates

Plantae



Mb: tissue O_2 receivers & storers; MONOMERS

Hb: O_2 transporters; usually **TETRAMERS** and/or COOPERATIVE

α_1, α_2 } Jeffreys says these are virtually identical and must be recent separation in humans. But mice also have duplication.

Polymorphism very high

β: Hb_A, Hb_C, Hb

paramyxov (see Snyder)

Phylogenetic distribution

- plants
- invertebrates

12.05.91

plesiomorphic

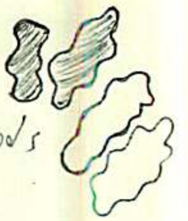
GGTACTGAA
GGAACCGTA
GATACTCTA

apomorphic

Comparative morphology : many judgement calls as to what is important

Molecular systematics: avoids problem of divergence in body plans as confusers of ~~sy~~ phylogeny

apomorphic : derived character



see Molecular Methods in Taxonomy

Two kinds of statistical approaches to this.

① distance methods

② parsimony or cladistics
- assumes shortest path

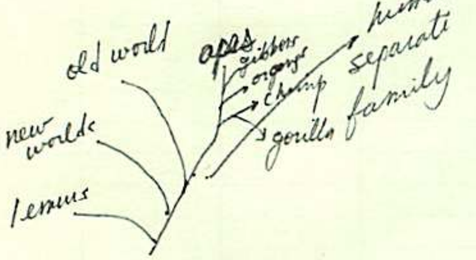
Problems

① how get time onto this

Atchley & Fitch Science 254:554-558

Primate phylogeny

Old view



New view
① humans & apes in same family

Pan Gorilla Homo