Why are you here?

	Structure	Complexity	Scale	Design
Foundations	Murray/ Csete	Parrilo	Bahmieh	Dahleh
Physics	Carlson	Mabuchi	Gillespie/ Petzold	Gershenfeld
Information	Low	Packard	Willinger	Paganini
Biology	Arkin	Savageau	Mitra	Khammash
(Moderators)	Kitano	Tsao	Jacobs	Glover

Matchmaking

Dep

EMORY
UNIVERSITY
SCHOOL OF
MEDICINE

Department of Anesthesiology

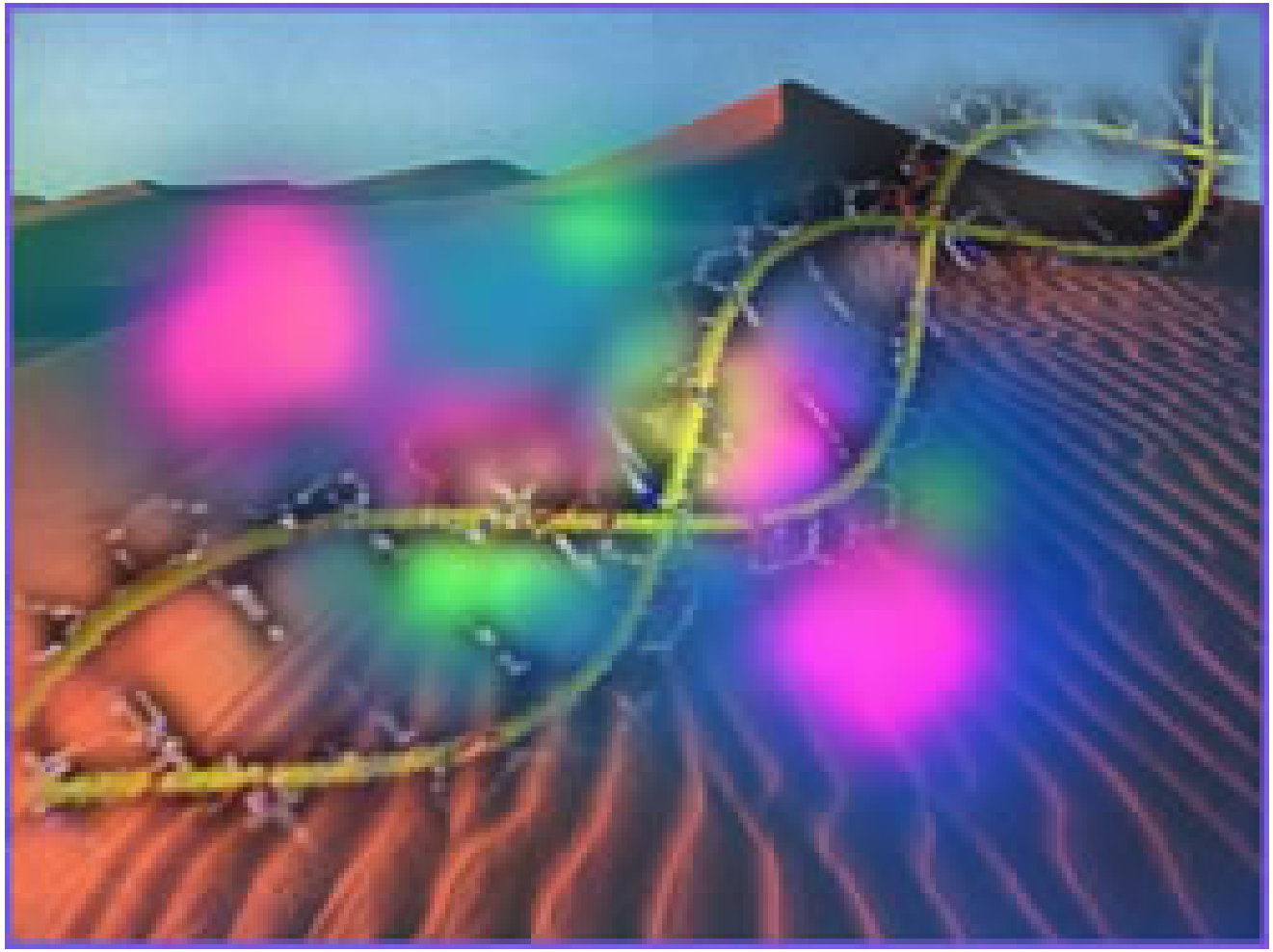
Little change?

Technology has enabled better vigilance

Controls will make homeostasis under anesthesia more controlled

BUT….that's the easy problem!

Genomic revolution has bypassed clinical anesthesiology?
Anesthesiology has avoided the genomic revolution?



Dep

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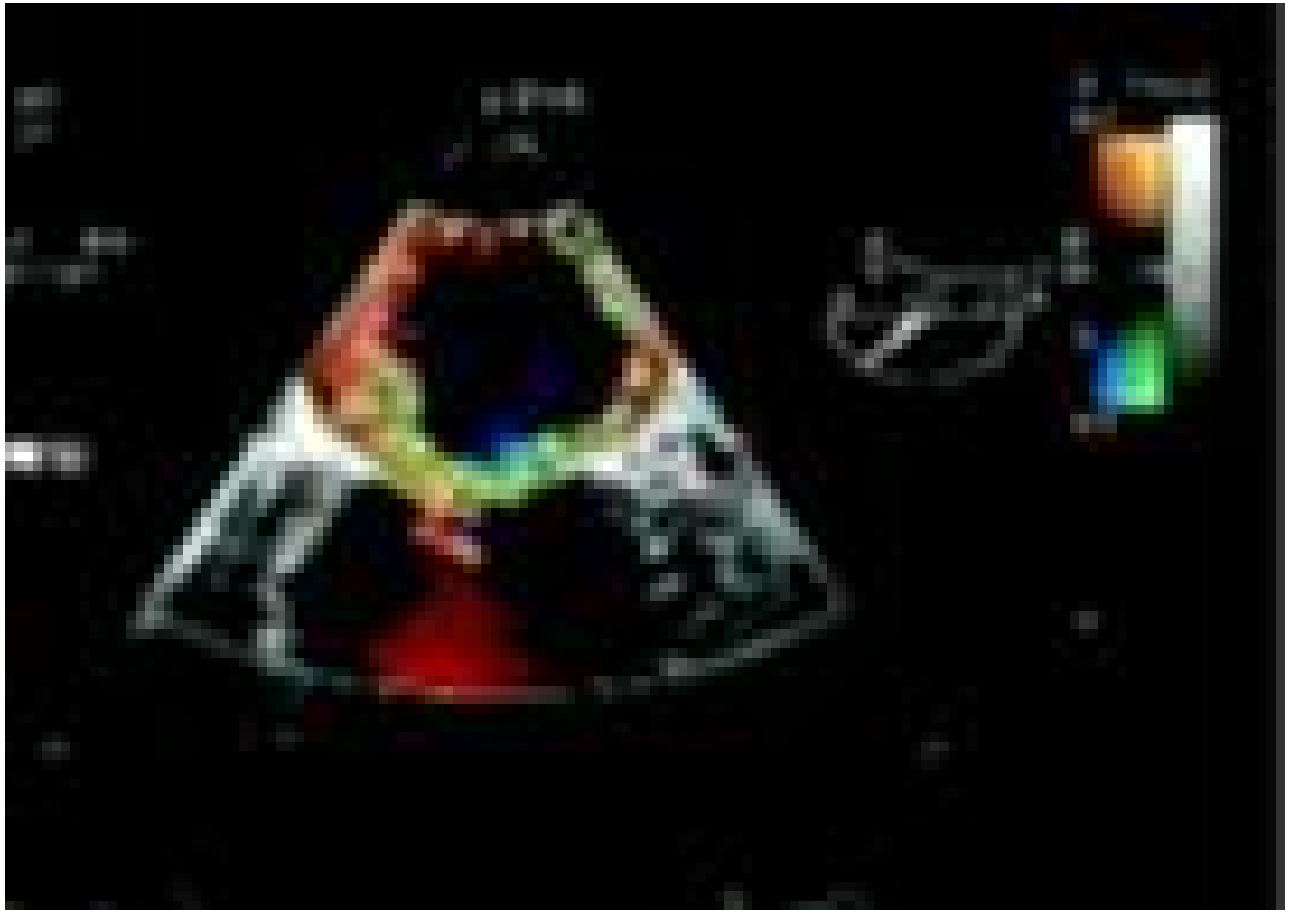
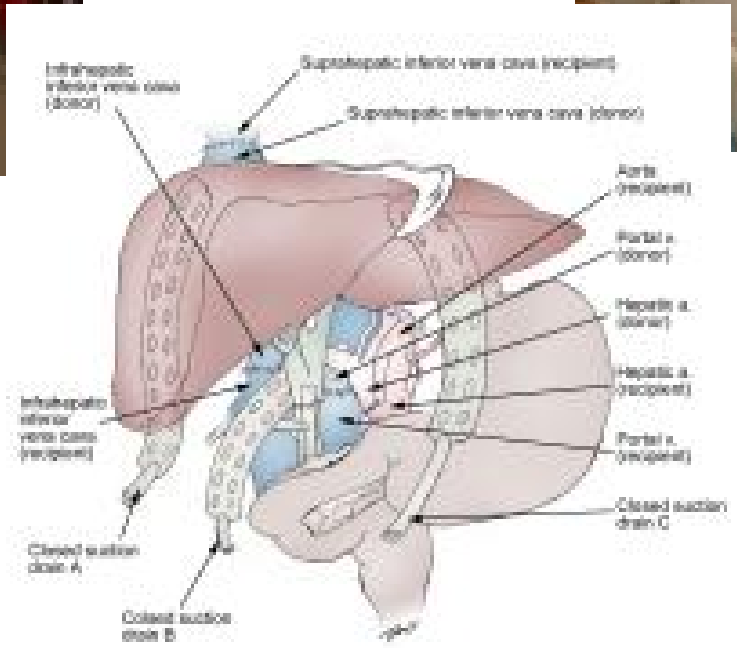
Department of Anesthesiology

Intuitive, hand-crafted assumptions allow pretty reasonable sedation algorithms



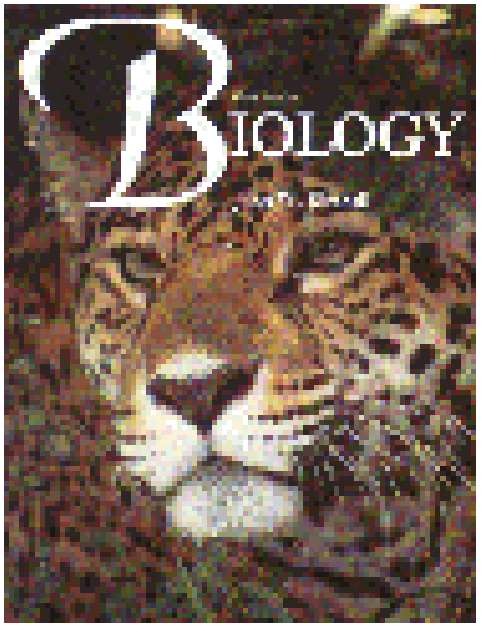
Controls will help here

(Dialing up and down is Distracting)



…but yet to be seen if will help here

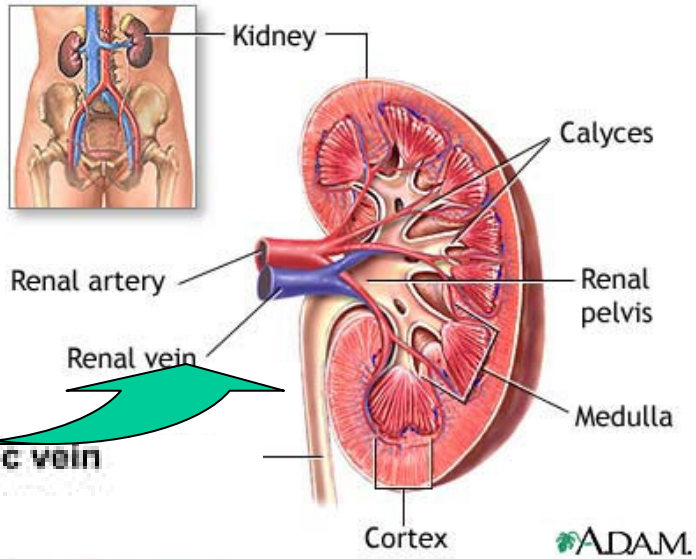
All our cues are indirect: We don't act on real mechanisms

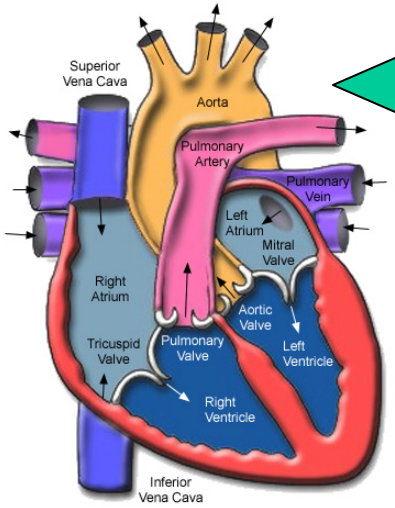

BIOLOGY

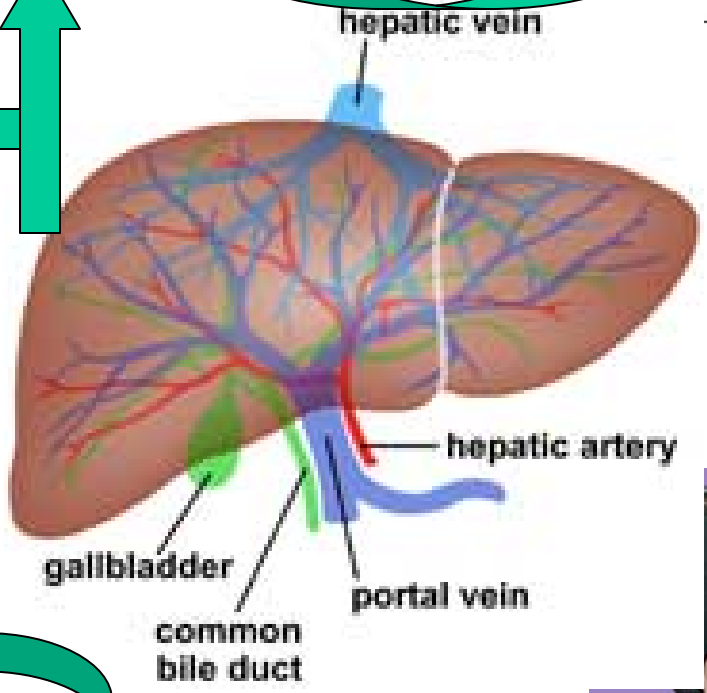
?

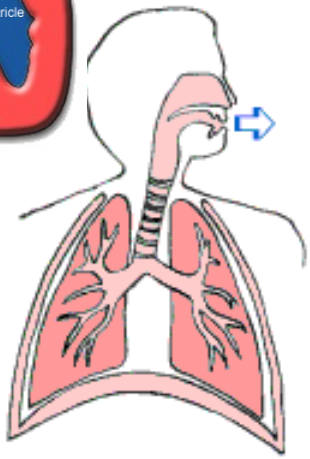
?

GREAT PHYSICIANS ACT ON THIS









NONE OF THIS IS IN A TEXTBOOK (of Medicine)

Instead scattered around medical and biology journals

Combination of clinical gut/eye/taste

…and basic science

The basic science is physiology (education crisis)

-completely controlled by feedback

Enormous clues exist in biology but the literature and language are not in contact with biologists

/translation="MMSSYKRATLDEEDLVDSLSEGDVYPNGLQVNFRSPRSGQRCWA
ARTSVEKRLVVLVTLLAAGLVACLAALGIQYRTRTPPVCLTEACVSVTSSILNSMDPT
VDPCQDFFSYACGGWIKANPVPDGHSRWGTFSNLWEHNQAIIKHLLENSTASASEAEK
KAQVYYRACMNETRIEELRAKPLMELIEKLGGWNITGPWAKDNFQDTLQVVTAHYRTS
PFFSVYVSADSKNSNSNVIQVDQSGLGLPSRDYYLNKTENEKVLTGYLNYMVQLGKLL
GGGDEDSIRPQMQQILDFETALANITIPQEKRRDEELIYHKVTAAELQTLAPAINWLP
FLNAIFYPVEINESEPIVVYDKEYLRQVSTLINSTDKCLLNNYMMWNLVRKTSSFLDQ
RFQDADEKFMEVMYGTKKTCLPRWKFCVSDTENNLGFALGPMFVKATFAEDSKNIASE
IILEIKKAFEESLSTLKWMDEDTRRSAKEKADAIYNMIGYPNFIMDPKELDKVFNDYT
AVPDLYFENAMRFFNFSWRVTADQLRKAPNRDQWSMTPPMVNAYYSPTKNEIVFPAGI
LQAPFYTRSSPNALNFGGIGVVVGHELTHAFDDQGREYDKDGNLRPWWKNSSVEAFKQ
QTECMVQQYNNYSVNGEPVNGRHTLGENIADNGGLKAAYRAYQNWVKKNGAEQILPTL
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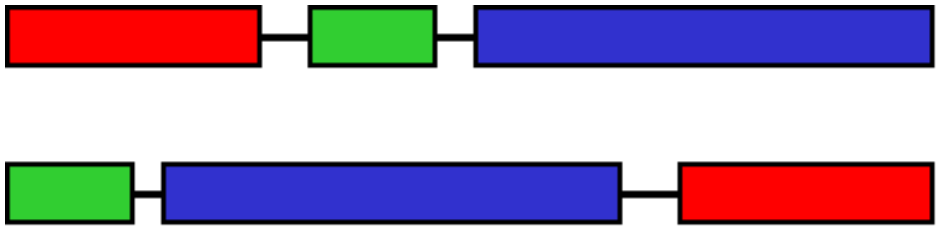
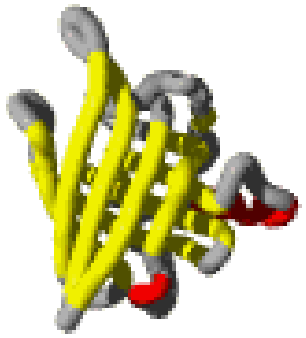
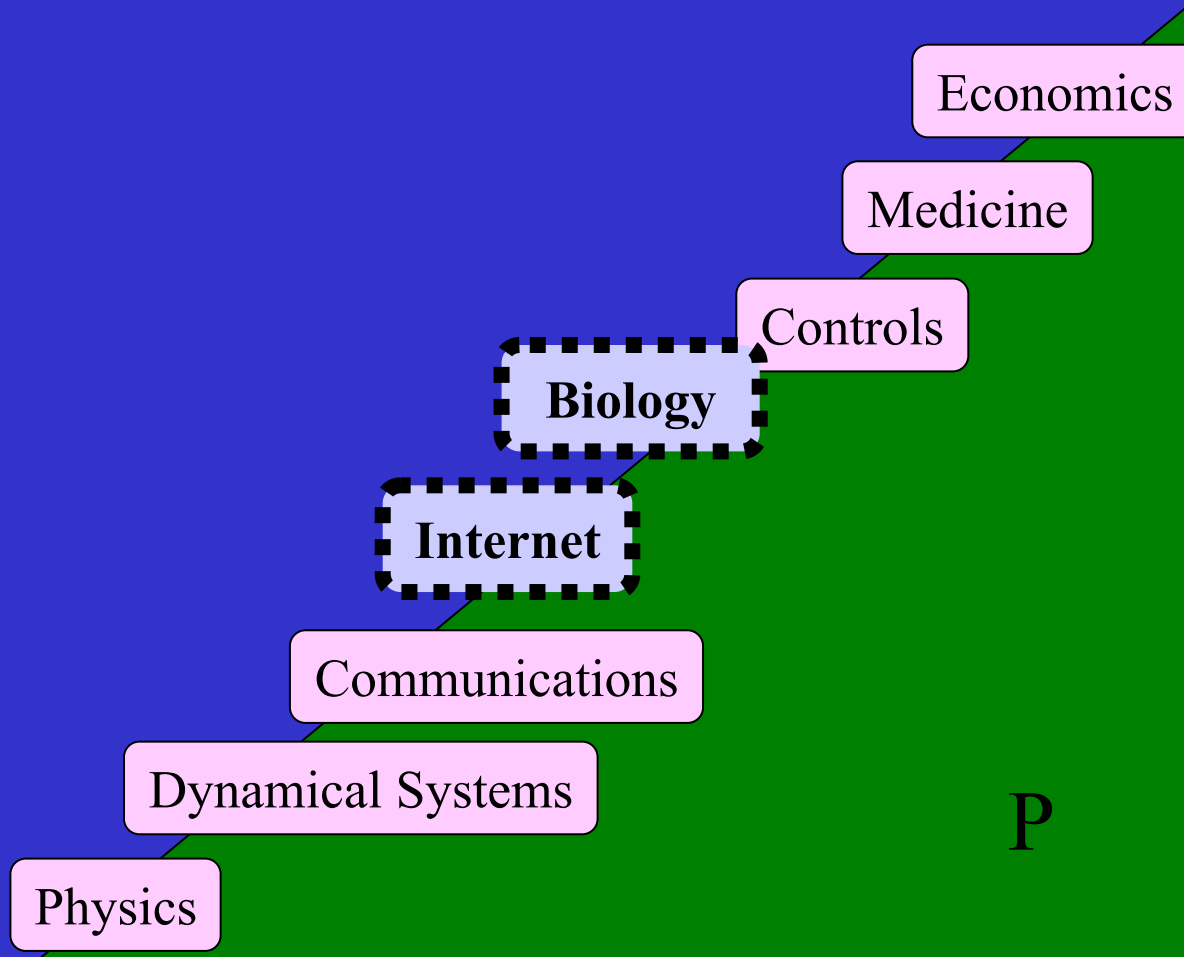
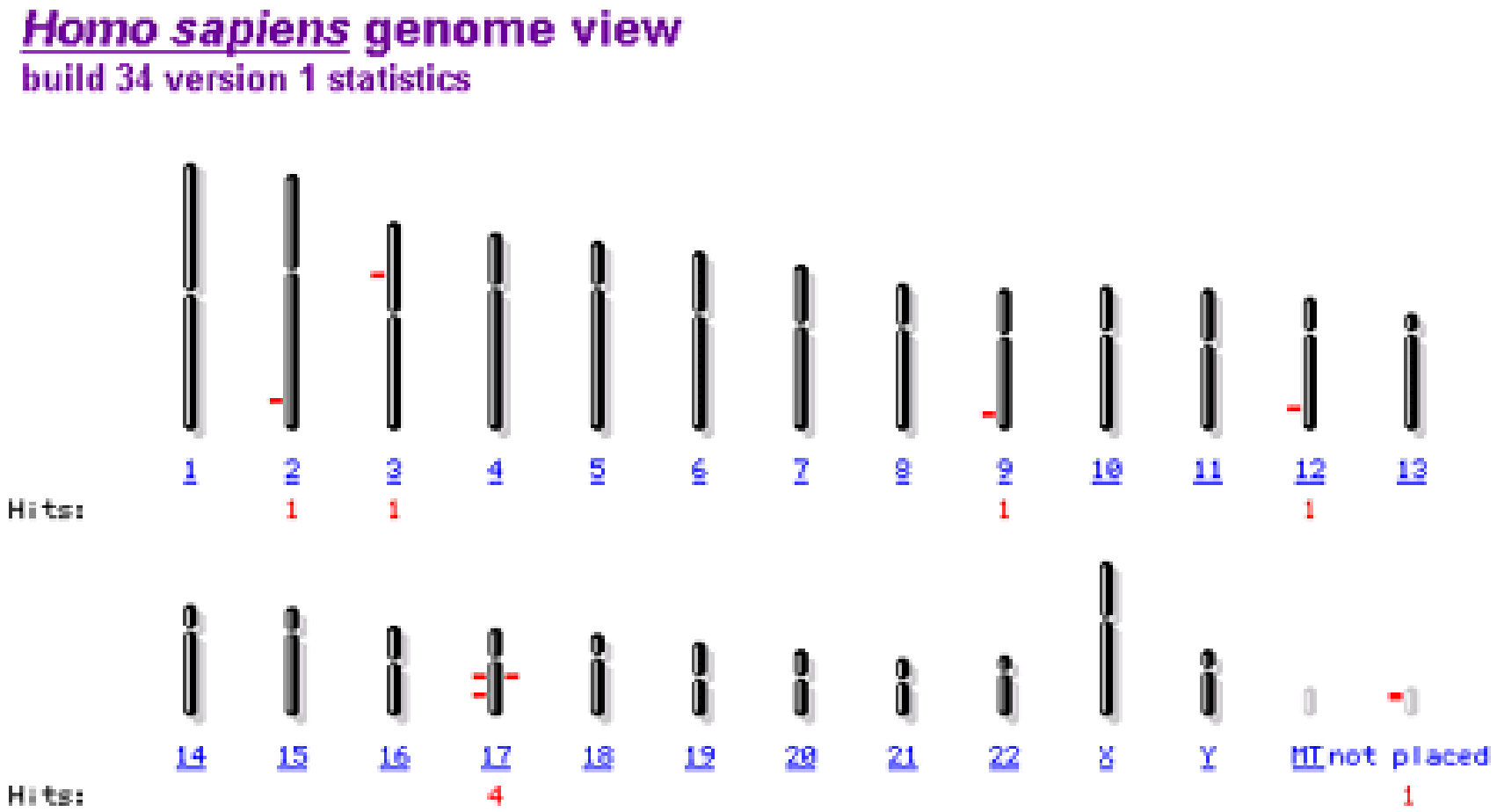




Elements of theories of complexity

- Modeling
- Simulation (NP)
- Analysis (coNP)
- Synthesis/design
- Hard limits/laws





Premature to jump here…

The biochemical basis of oxygen-mediated phenotypic changes?

So fundamental

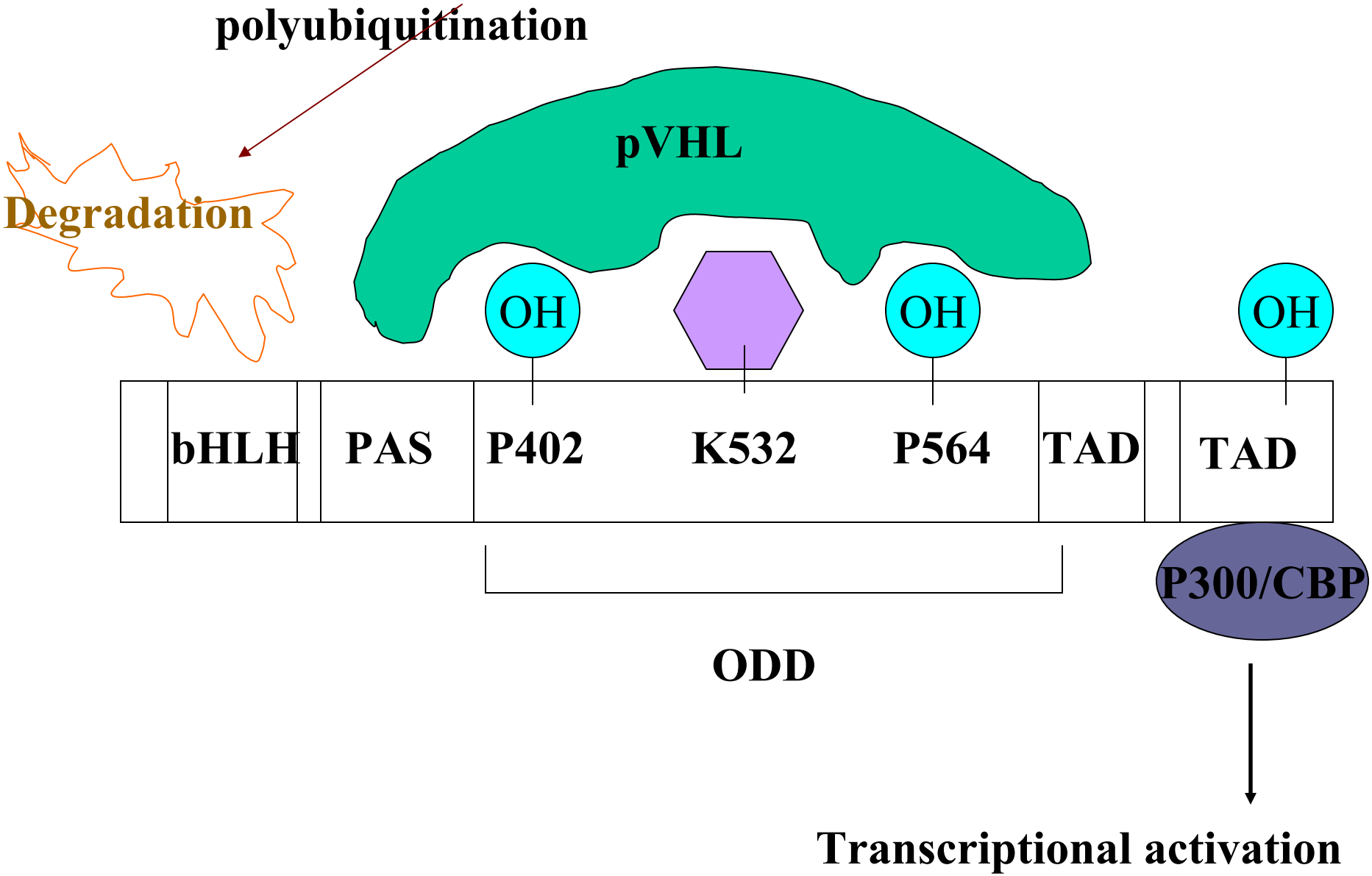
- Medicine (Anestheisology) obviously makes oxygen availability/ management a priority
- Anesthesia A,B,C (Airway, Breathing, Circulation)
- But the elegant biological context of oxygen regulation is not part of medical dialogue

O2 regulated by feedback

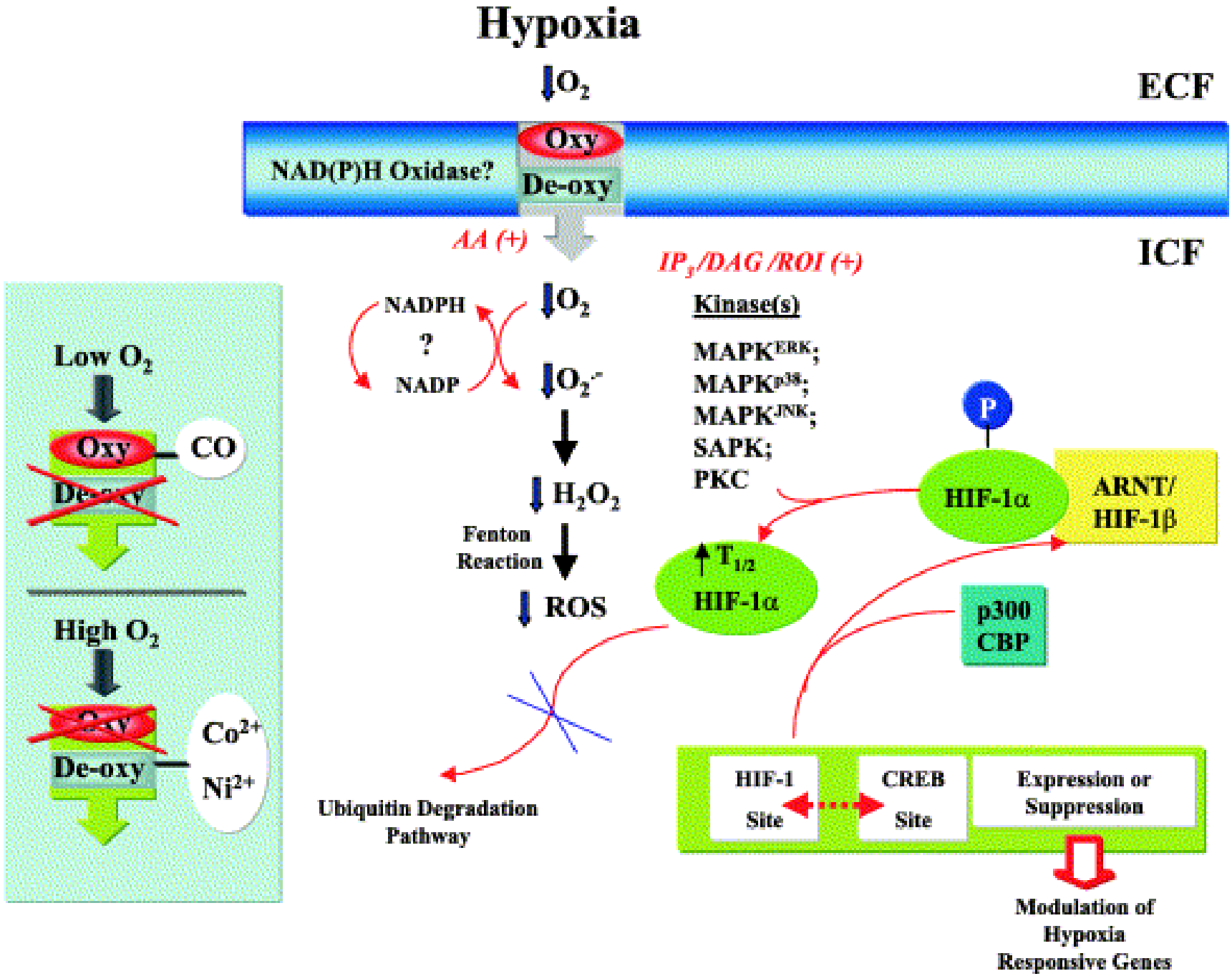
- LOW O2: REGULATES COMPLEX DEVELOPMENT
- Breath more (hypoxic ventilatory drive)
- Use less energy (glycolytic pathways)
- Dilate the blood supply (NO, CO)
- Grow new blood vessels (VEGF)
- Make more red cells to carry oxygen (EPO)
- QUIETLY GOES ON IN ALL CELLS IN ALL CONDITIONS, ALL OF THE TIME

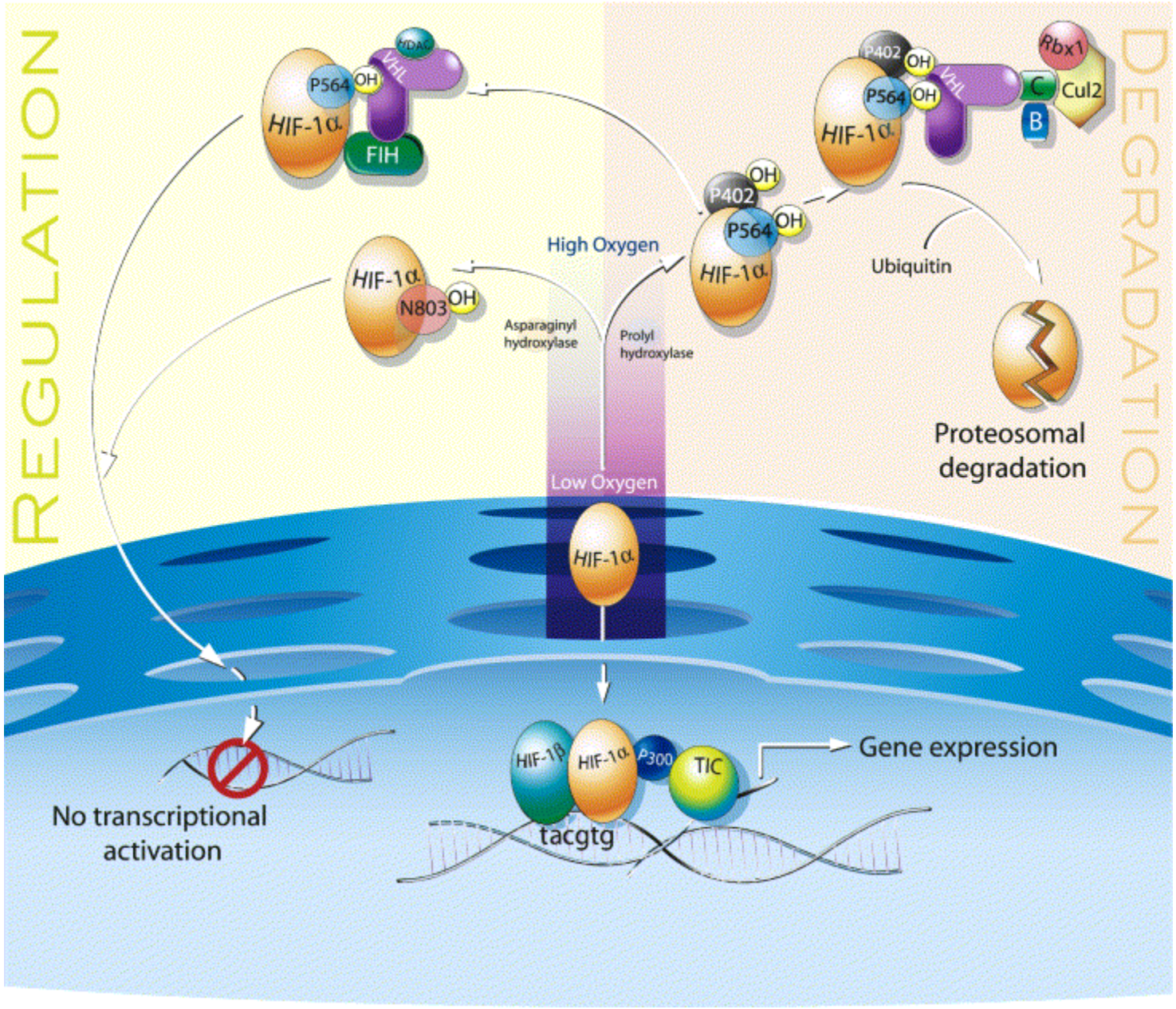
Normoxia

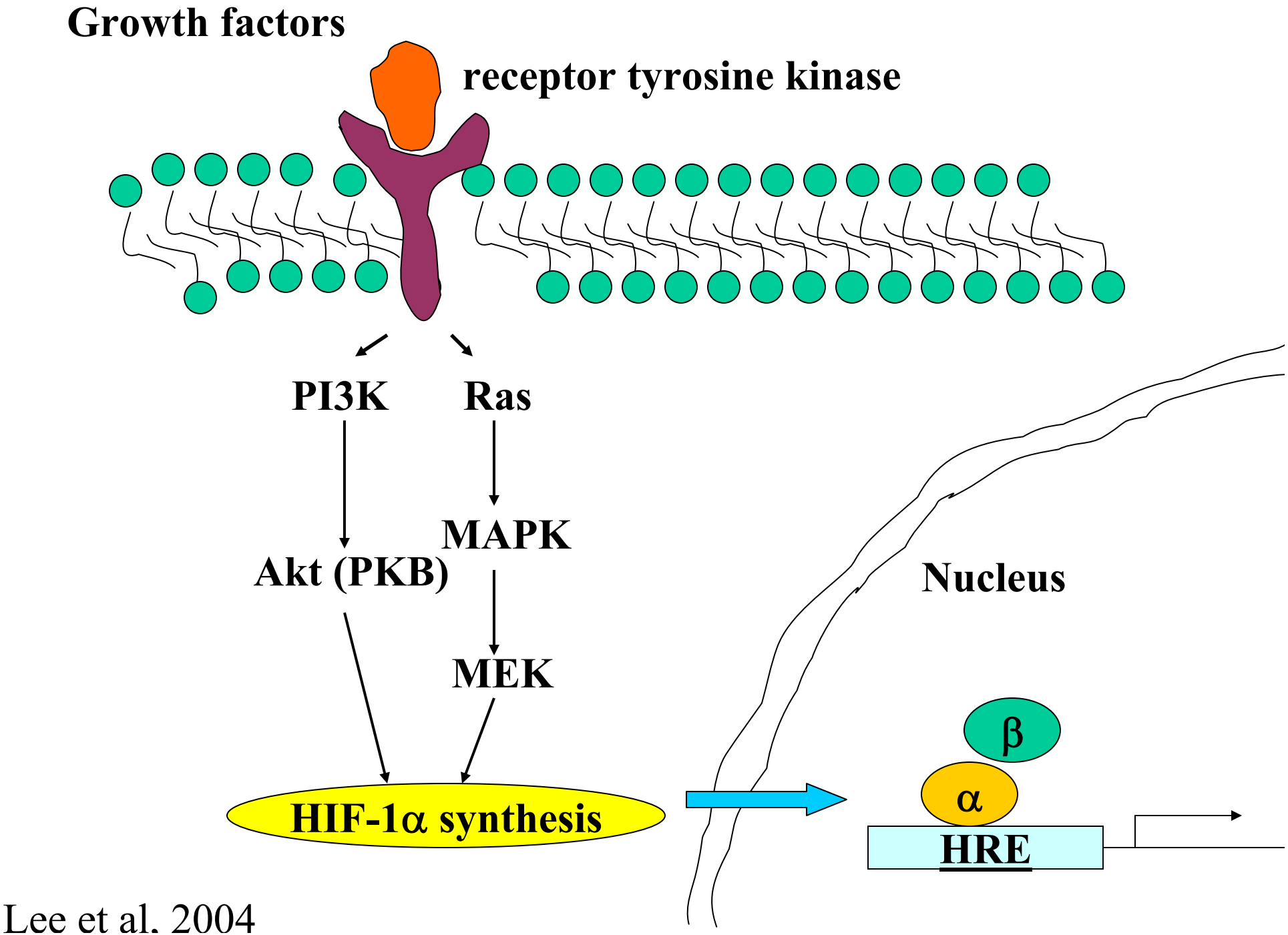
HIF 1 alpha



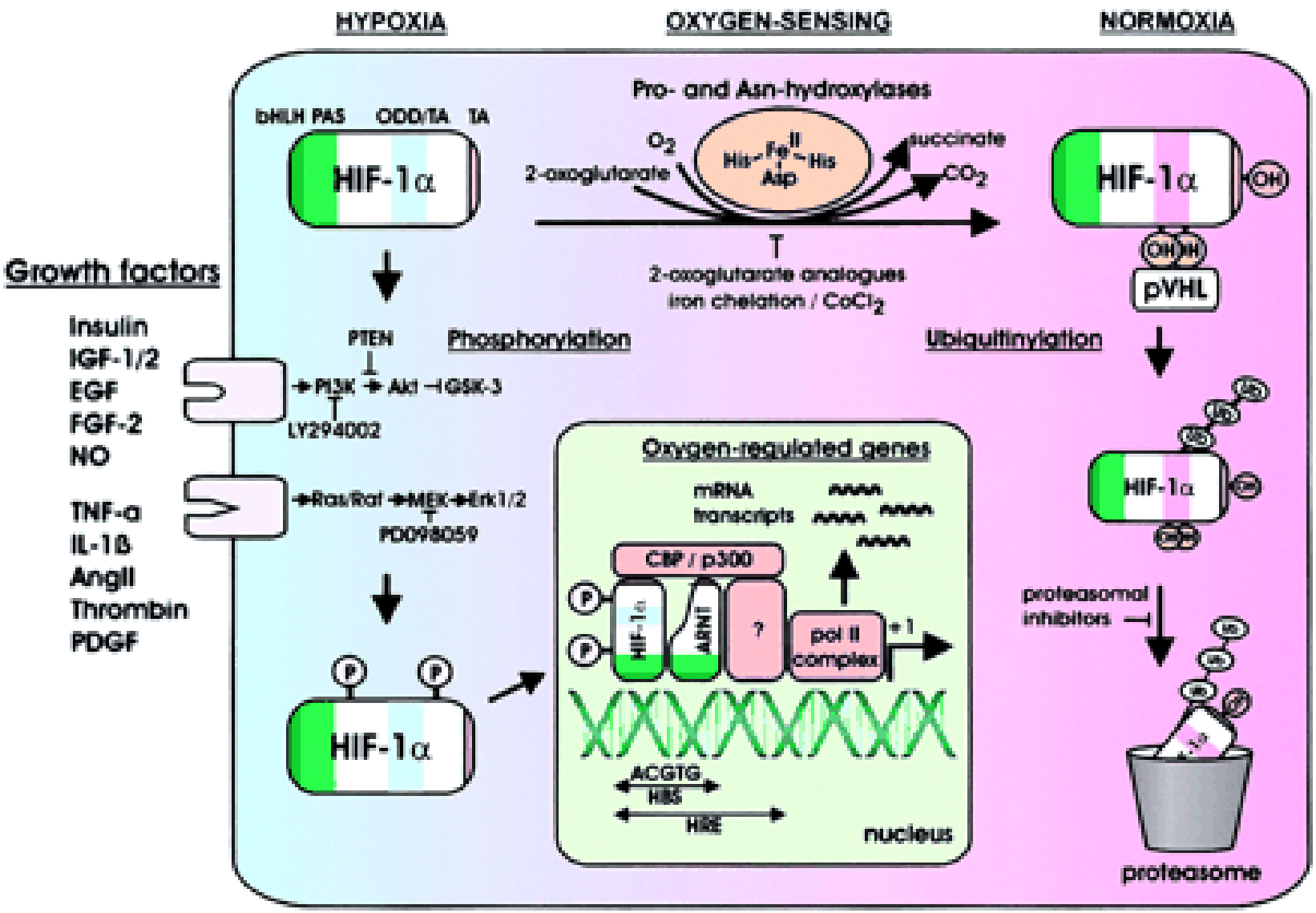
Lee et al, 2004


Hypoxia
O_2
ECF
Oxy
NAD(P)H Oxidase?
De-oxy
AA (+)
ICF
IP_3/DAG /ROI (+)
NADPH
?
NADP
O_2
$O_2^{\cdot-}$
H_2O_2
Fenton Reaction
ROS
Kinase(s)
$MAPK^{ERK}$;
$MAPK^{p38}$;
$MAPK^{JNK}$;
SAPK;
PKC
P
HIF-1α
ARNT/
HIF-1β
$T_{1/2}$
HIF-1α
p300
CBP
Low O_2
Oxy
CO
De-oxy
High O_2
Oxy
Co^{2+}
Ni^{2+}
De-oxy
Ubiquitin Degradation Pathway
HIF-1 Site
CREB Site
Expression or Suppression
Modulation of Hypoxia Responsive Genes

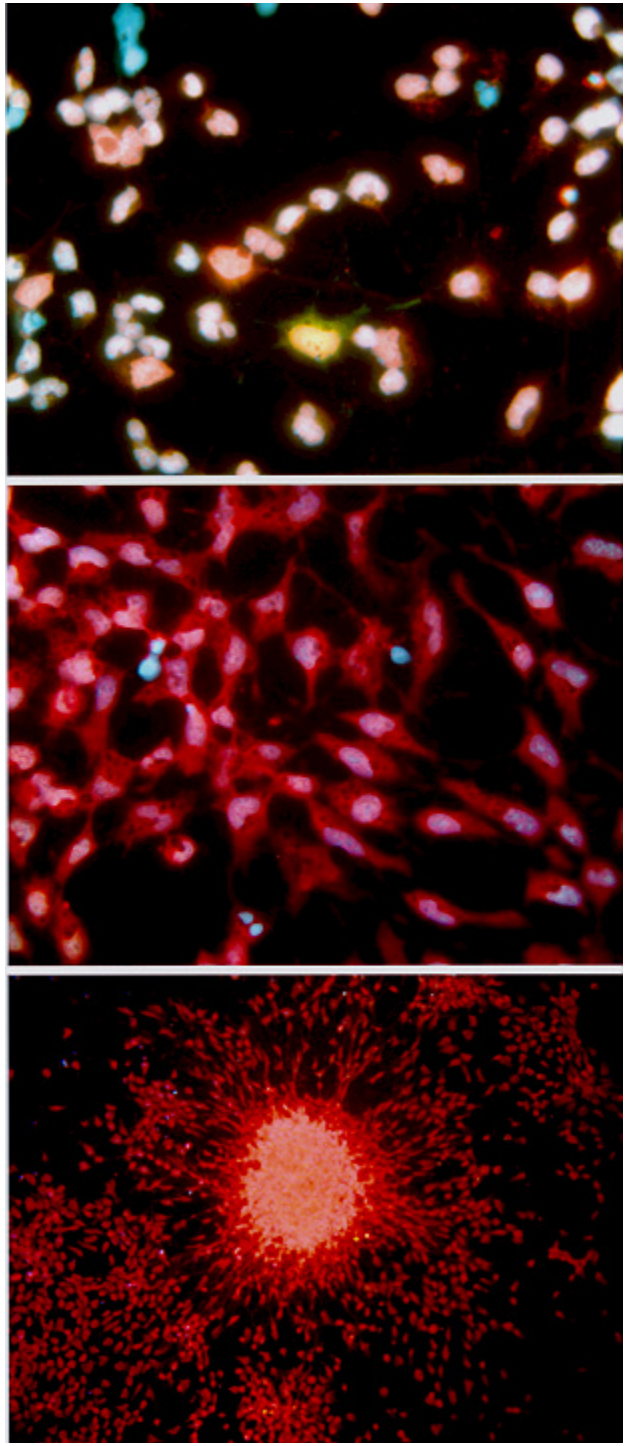

REGULATION
DEGRADATION
HIF-1α
P564
OH
VHL
pVBA
FIH
HIF-1α
N803
OH
High Oxygen
Asparaginyl hydroxylase
Prolyl hydroxylase
HIF-1α
P402
OH
P564
OH
VHL
Rbx1
C
Cul2
B
Ubiquitin
Proteosomal degradation
Low Oxygen
HIF-1α
No transcriptional activation
HIF-1β
HIF-1α
P300
TIC
Gene expression
tacgtg



Lee et al. 2004


HYPOXIA
OXYGEN-SENSING
NORMOXIA
Pro- and Asn-hydroxylases
bHLH PAS ODD/TA TA
HIF-1α
O2
2-oxoglutarate
His Fe II His
Asp
succinate
CO2
2-oxoglutarate analogues
iron chelation / CoCl2
HIF-1α
OH
OH OH
pVHL
Growth factors
Insulin
IGF-1/2
EGF
FGF-2
NO
TNF-α
IL-1ß
AngII
Thrombin
PDGF
PTEN
PI3K
Akt
GSK-3
LY294002
Phosphorylation
Ubiquitinylation
Ras/Raf
MEK
Erk1/2
PD098059
Oxygen-regulated genes
mRNA transcripts
CBP / p300
HIF-1α
ARNT
?
pol II complex
+1
P
ACGTG
HBS
HRE
nucleus
HIF-1α
proteasomal inhibitors
proteasome

VHL

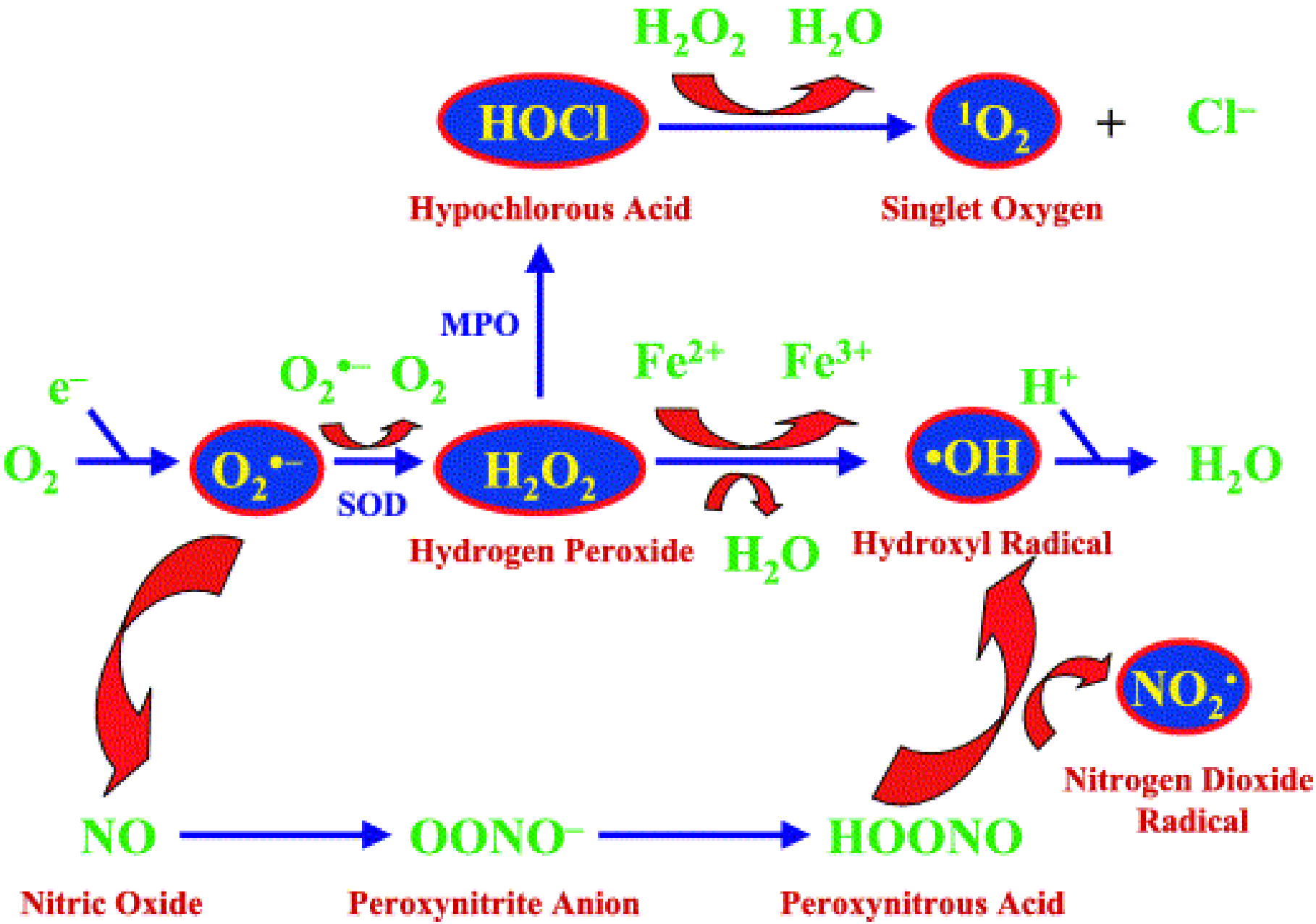


2% O2

20% O2

O2 vs. ROS (reactive O2 species)

- HIF-1 expression modulated by ROS
- HIF-1 expression modulated by NO
- Hypoxic ventilatory drive is driven by SNO (S-nitrosothiols) rather than O2
- Glucose regulation of HIF-1
- Redox regulation of transcription independent of HIF-1

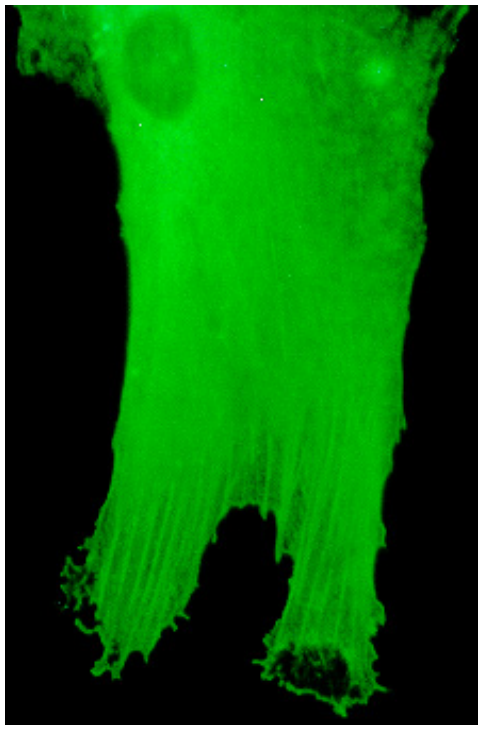

H_2O_2 H_2O
HOCl
$^1O_2$
+
Cl^-
Hypochlorous Acid
Singlet Oxygen
MPO
e^-
O_2
$O_2^{\bullet-}$ O_2
$O_2^{\bullet-}$
SOD
H_2O_2
Fe^{2+} Fe^{3+}
H^+
•OH
H_2O
Hydrogen Peroxide
H_2O
Hydroxyl Radical
$NO_2^{\bullet}$
Nitrogen Dioxide Radical
NO
OONO⁻
HOONO
Nitric Oxide
Peroxynitrite Anion
Peroxynitrous Acid

HIF as fundamental

- Cloned in 1996 (by a clinician)
- Recent visit to Mayo clinic: The prettiest story in biology
- (Complexity in medicine/biology is invisible—except for pain)

- Most defects in HIF process are EARLY embryonic lethal
- Lessons for early human development?

Is HIF-1 (and its regulation)



A protocol?
A module?
A law?

IMPORTANT:
-Faciltilates, optimizes complex development
-Retained to faciltiate plasticity (altitude, exercise, disease)…Robustness
-Its retention as a highly tuned system promotes cancer, chemotherapy resistance and metastases
-VHL…Fragility

WHY ARE YOU HERE?

Physics/Computer science/Biology/Economics
…don't talk

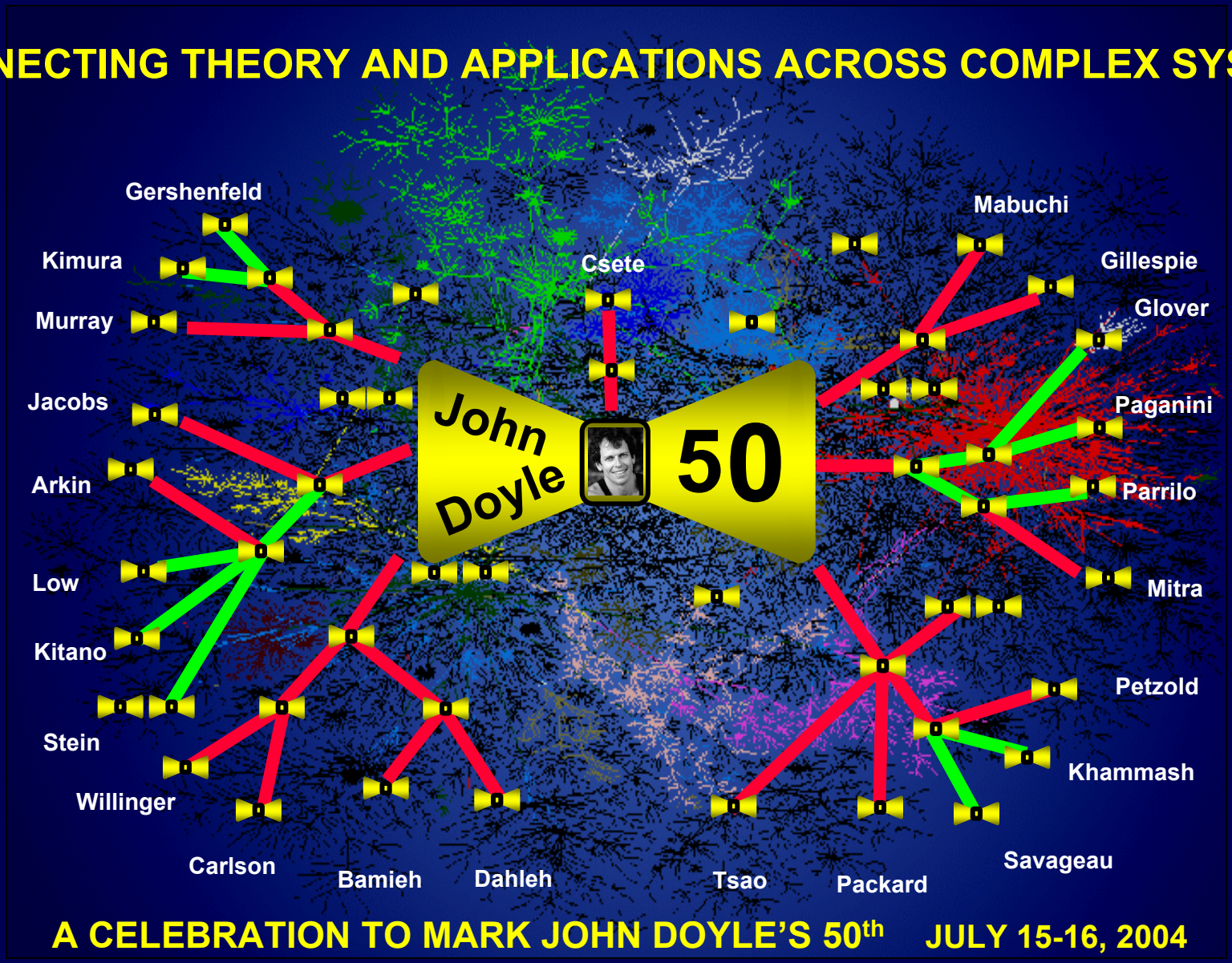
Biology and Medicine have a huge wall between them
→language (and style)
→most complexity in both is feedback
→the most glaring communication gap between sciences
→mathematics is necessary to bridge the gap

Do Steven's models of the internet inform HIF-1?
Do Hana's bacterial heat shock models inform miscues in the HIF response that are oncogenic?

Connections

Foundations and Edges

CONNECTING THEORY AND APPLICATIONS ACROSS COMPLEX SYSTEMS



A CELEBRATION TO MARK JOHN DOYLE'S 50th JULY 15-16, 2004

Thanks!