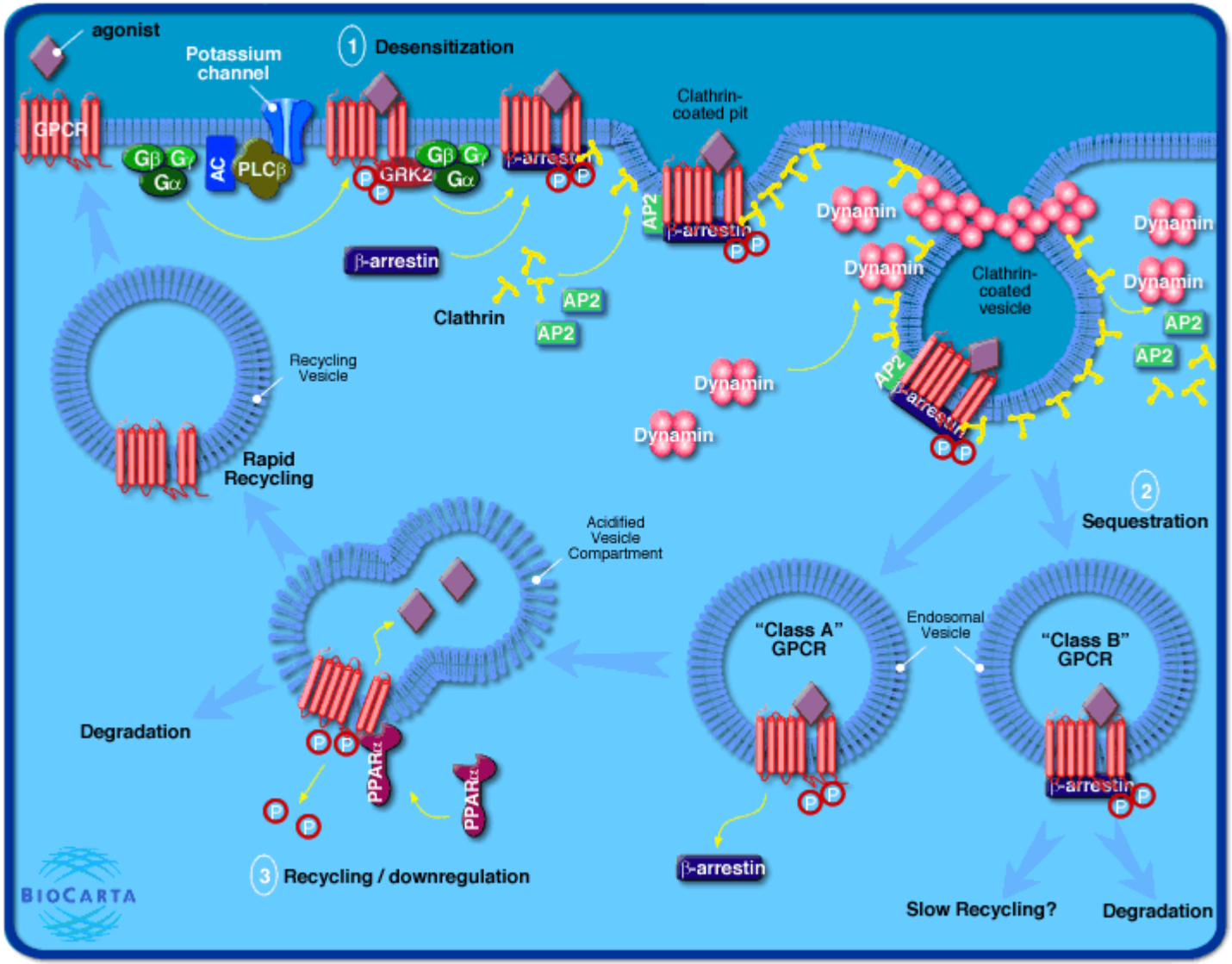
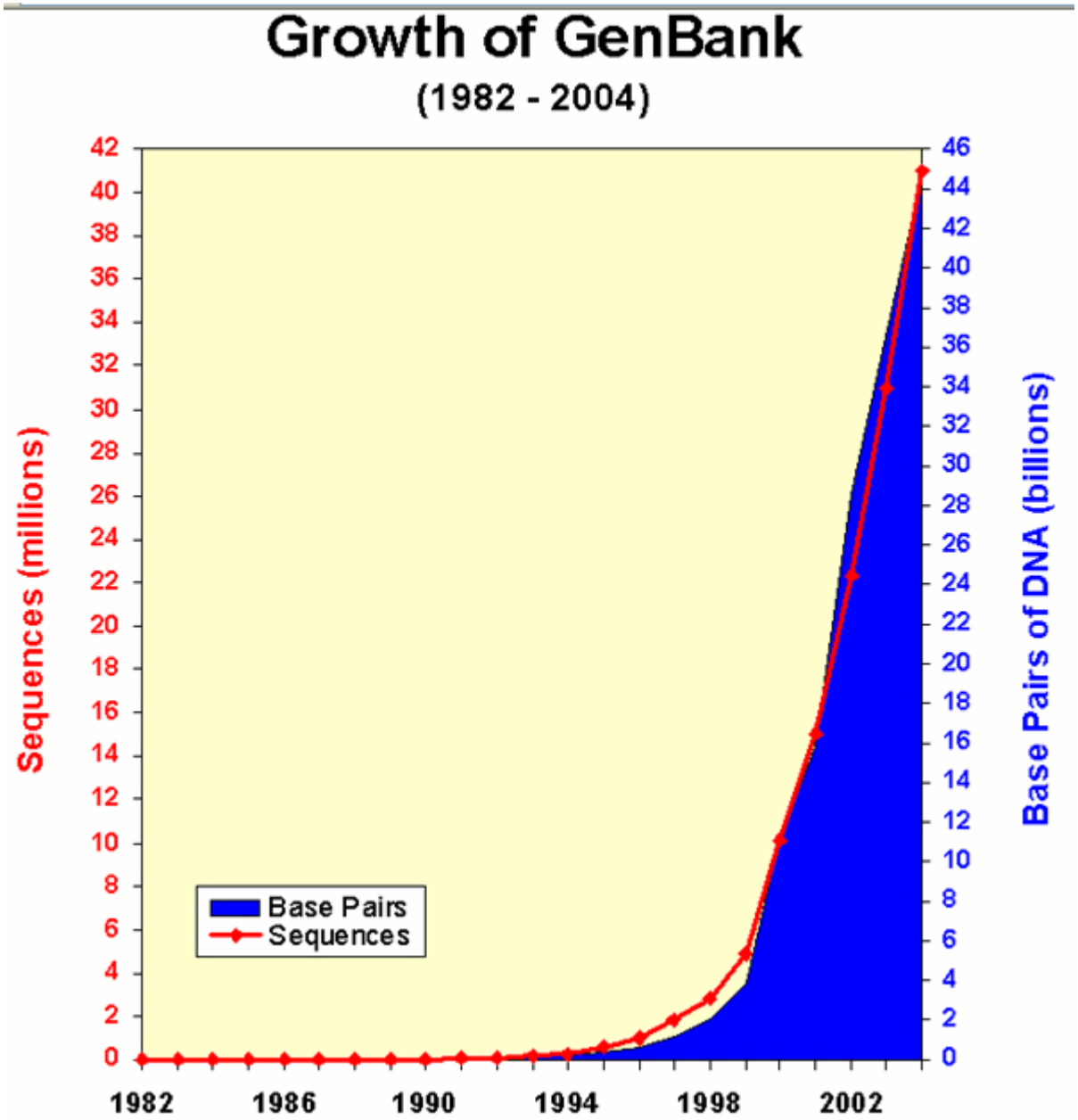
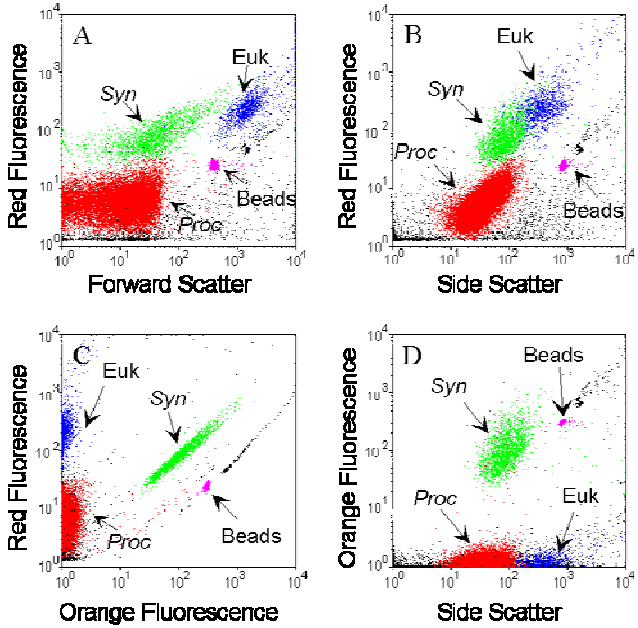
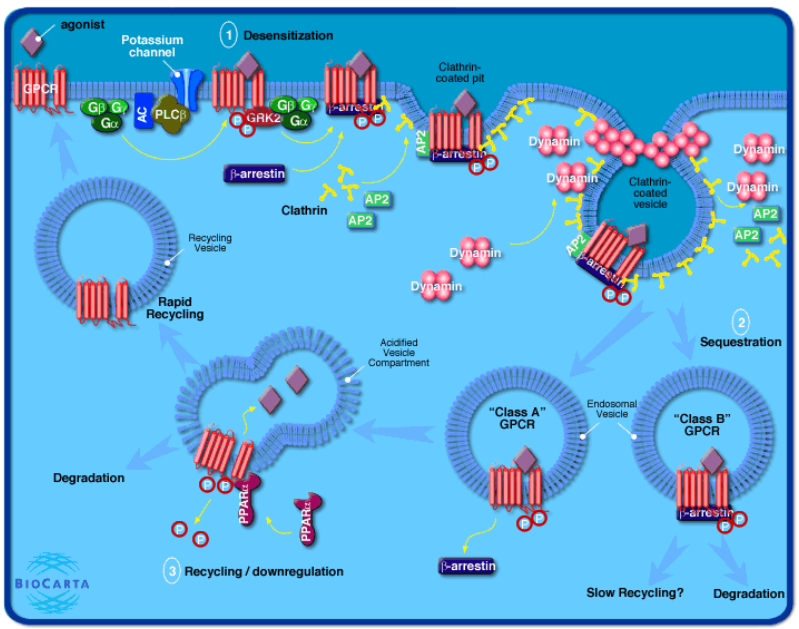
ß-arrestins in GPCR Desensitization

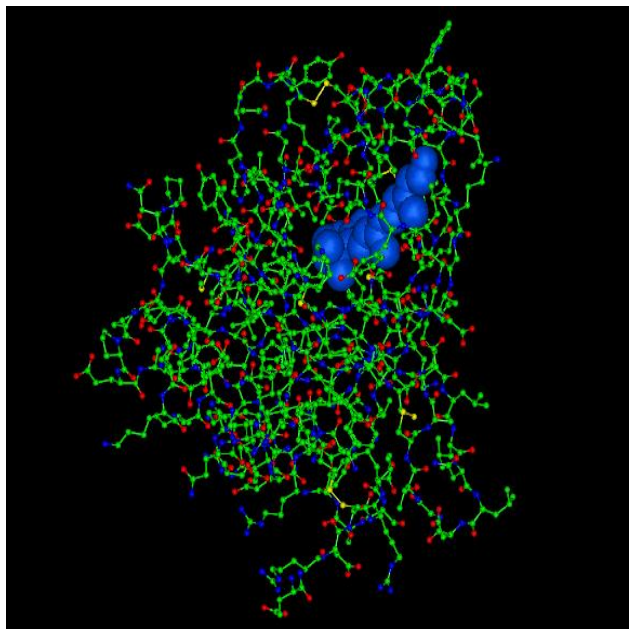


How Lisp Will Save the World


Growth of GenBank
(1982 - 2004)
Sequences (millions)
Base Pairs of DNA (billions)
Base Pairs
Sequences
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40
42
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40
42
44
46
1982
1986
1990
1994
1998
2002

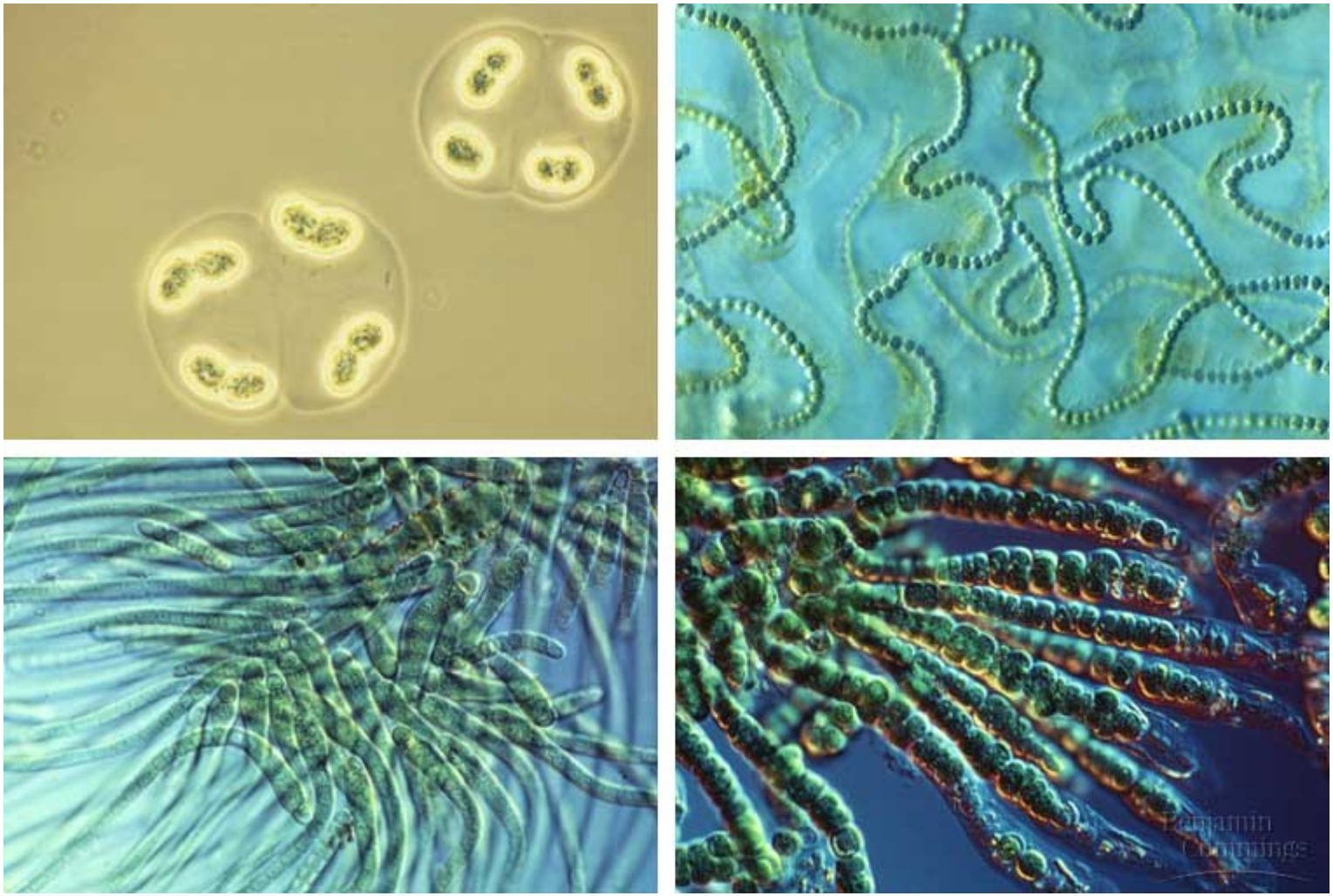

A
Euk
Syn
Beads
Proc
Red Fluorescence
Forward Scatter
B
Euk
Syn
Proc
Beads
Red Fluorescence
Side Scatter
C
Euk
Syn
Proc
Beads
Red Fluorescence
Orange Fluorescence
D
Beads
Syn
Proc
Euk
Orange Fluorescence
Side Scatter


agonist
Potassium channel
1 Desensitization
GPCR
Gβ Gγ Gα
AC
PLCβ
GRK2
β-arrestin
Clathrin-coated pit
AP2
Clathrin
Dynamin
Clathrin-coated vesicle
Recycling Vesicle
Rapid Recycling
Acidified Vesicle Compartment
2 Sequestration
Degradation
PPARα
"Class A" GPCR
Endosomal Vesicle
"Class B" GPCR
3 Recycling / downregulation
Slow Recycling?
Degradation
BIOCARTA

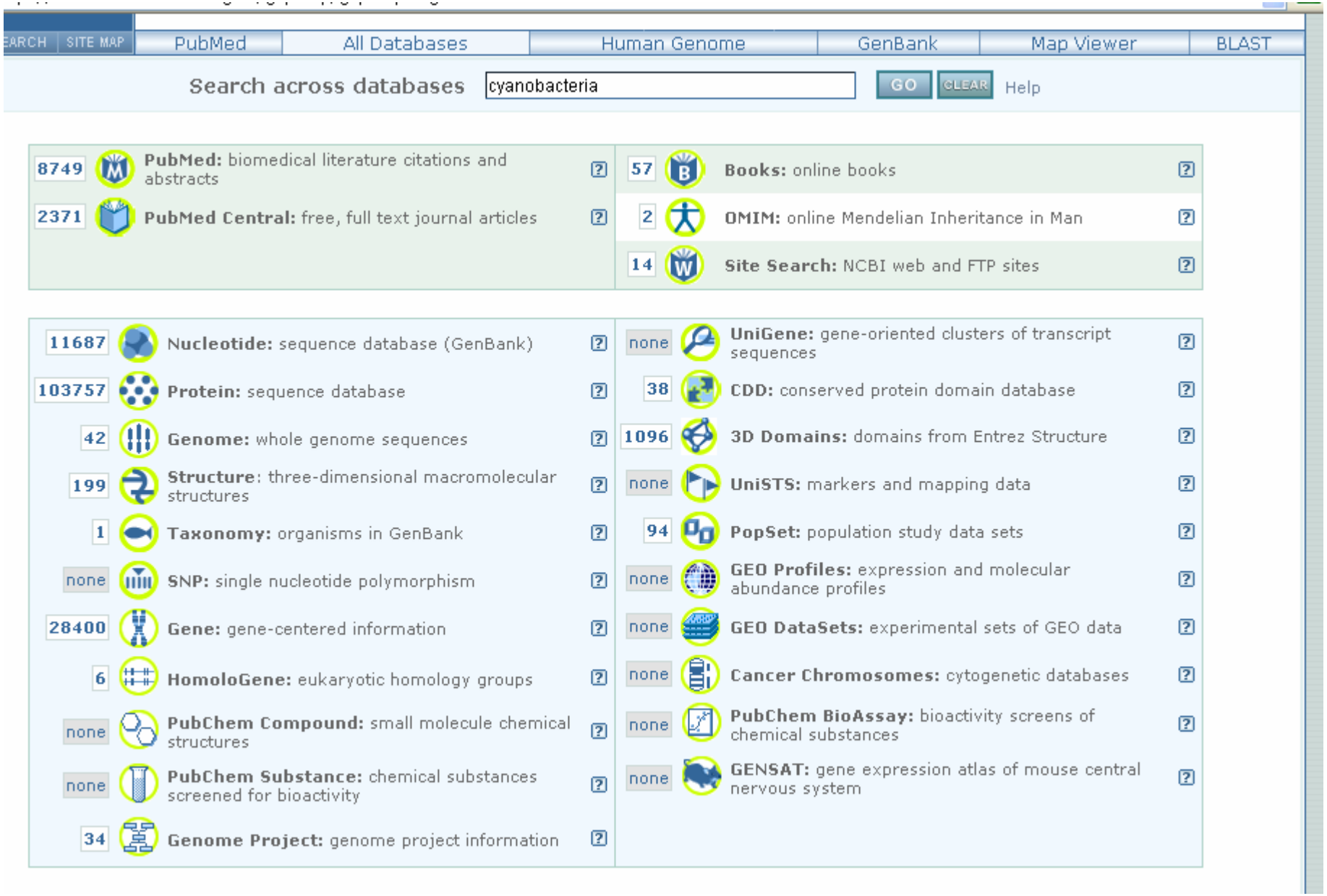


15,596,125 abstracts

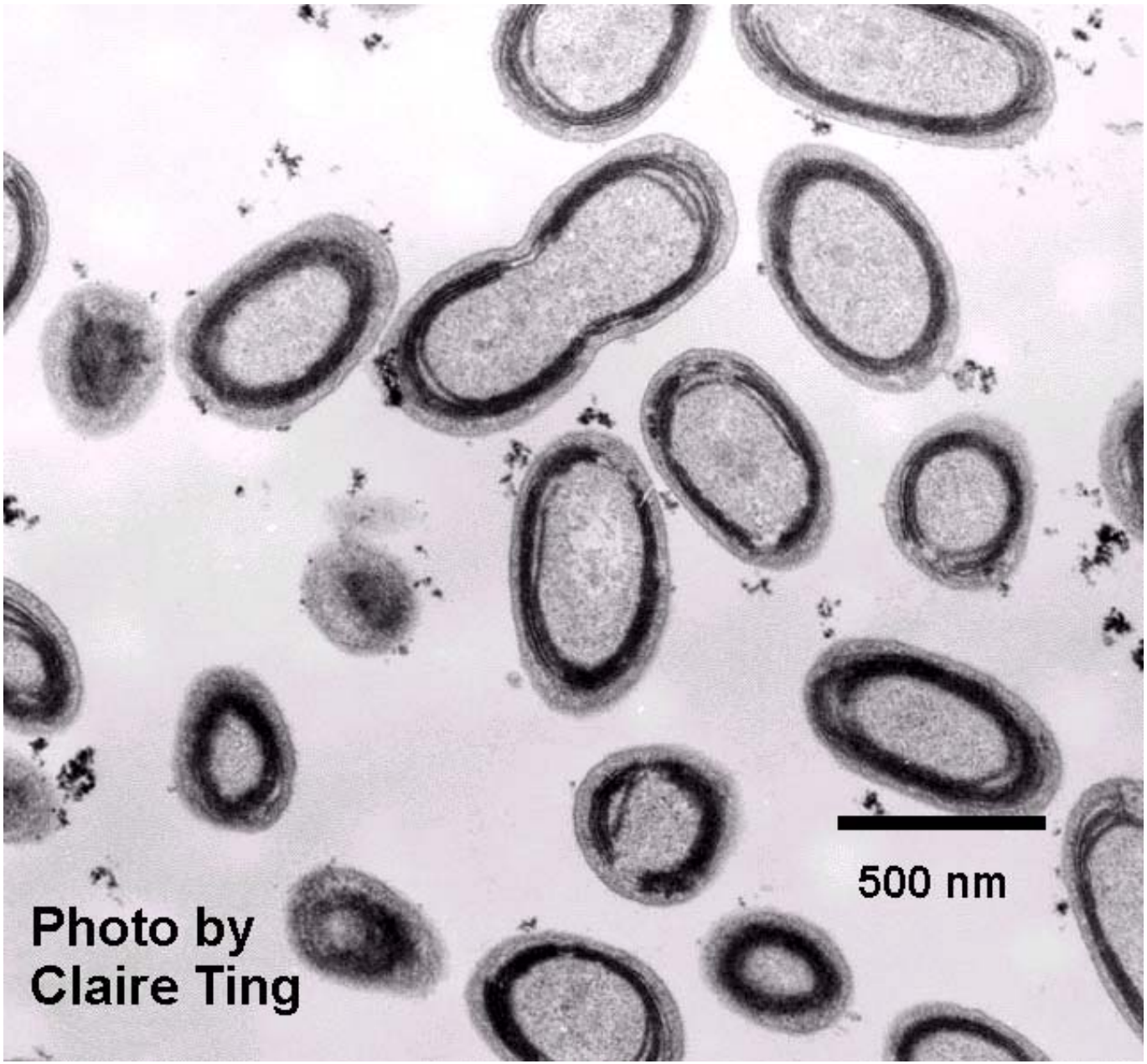
Cyanobacteria



http://www.anselm.edu/homepage/jpitocch/genbios/27-11x1-Cyanobacteria.jpg


SITE MAP
PubMed
All Databases
Human Genome
GenBank
Map Viewer
BLAST
Search across databases
cyanobacteria
GO
CLEAR
Help
8749 PubMed: biomedical literature citations and abstracts
2371 PubMed Central: free, full text journal articles
57 Books: online books
2 OMIM: online Mendelian Inheritance in Man
14 Site Search: NCBI web and FTP sites
11687 Nucleotide: sequence database (GenBank)
103757 Protein: sequence database
42 Genome: whole genome sequences
199 Structure: three-dimensional macromolecular structures
1 Taxonomy: organisms in GenBank
none SNP: single nucleotide polymorphism
28400 Gene: gene-centered information
6 HomoloGene: eukaryotic homology groups
none PubChem Compound: small molecule chemical structures
none PubChem Substance: chemical substances screened for bioactivity
34 Genome Project: genome project information
none UniGene: gene-oriented clusters of transcript sequences
38 CDD: conserved protein domain database
1096 3D Domains: domains from Entrez Structure
none UniSTS: markers and mapping data
94 PopSet: population study data sets
none GEO Profiles: expression and molecular abundance profiles
none GEO DataSets: experimental sets of GEO data
none Cancer Chromosomes: cytogenetic databases
none PubChem BioAssay: bioactivity screens of chemical substances
none GENSAT: gene expression atlas of mouse central nervous system

Prochlorococcus



Tools for Thought

Table 1. Mathematical model of the budding yeast cell cycle

Equations governing cyclin-dependent kinases — Notes

$$\frac{d}{dt}[Cln2] = (k'_{s,n2} + k''_{s,n2}[SBF]) \cdot mass - k_{d,n2}[Cln2]$$

$$\frac{d}{dt}[Clb2]_T = (k'_{s,b2} + k''_{s,b2}[Mcm1]) \cdot mass - V_{d,b2}[Clb2]_T,\ V_{d,b2} = k'_{d,b2}([Hct1]_T - [Hct1]) + k''_{d,b2}[Hct1] + k'''_{d,b2}[Cdc20]$$

$$\frac{d}{dt}[Clb5]_T = (k'_{s,b5} + k''_{s,b5}[MBF]) \cdot mass - V_{d,b5} \cdot [Clb5]_T,\ V_{d,b5} = k'_{d,b5} + k''_{d,b5}[Cdc20]$$ — a

$$[Bck2] = [Bck2]^0 \cdot mass, \qquad [Cln3]^* = [Cln3]_{max} \frac{D_{n3} \cdot mass}{J_{n3} + D_{n3} \cdot mass}$$

$$[Clb2]_T = [Clb2] + [Clb2/Sic1], \quad [Clb5]_T = [Clb5] + [Clb5/Sic1]$$

$$[Sic1]_T = [Sic1] + [Clb2/Sic1] + [Clb5/Sic1]$$

Equations governing the inhibitor of Clb-dependent kinases

$$\frac{d}{dt}[Sic1]_T = k'_{s,c1} + k''_{s,c1}[Swi5] - \left(k_{d1,c1} + \frac{V_{d2,c1}}{J_{d2,c1} + [Sic1]_T}\right) \cdot [Sic1]_T$$ — b

$$\frac{d}{dt}[Clb2/Sic1] = k_{as,b2}[Clb2] \cdot [Sic1] - \left(k_{di,b2} + V_{d,b2} + k_{d1,c1} + \frac{V_{d2,c1}}{J_{d2,c1} + [Sic1]_T}\right) \cdot [Clb2/Sic1]$$

$$\frac{d}{dt}[Clb5/Sic1] = k_{as,b5}[Clb5] \cdot [Sic1] - \left(k_{di,b5} + V_{d,b5} + k_{d1,c1} + \frac{V_{d2,c1}}{J_{d2,c1} + [Sic1]_T}\right) \cdot [Clb5/Sic1]$$

$$V_{d2,c1} = k_{d2,c1}(\varepsilon_{c1,n3}[Cln3]^* + \varepsilon_{c1,bk2}[Bck2] + [Cln2] + \varepsilon_{c1,b5}[Clb5] + \varepsilon_{c1,b2}[Clb2])$$

Equations governing the Clb degradation machinery

$$\frac{d}{dt}[Cdc20]_T = (k'_{s,20} + k''_{s,20}[Clb2]) - k_{d,20}[Cdc20]_T$$

$$\frac{d}{dt}[Cdc20] = k_{a,20}([Cdc20]_T - [Cdc20]) - (V_{i,20} + k_{d,20}) \cdot [Cdc20]$$

$$V_{i,20} = \begin{cases} k'_{i,20}, & \text{for END\_M} + 12\ \text{min} < t < \text{START\_S} \\ k''_{i,20}, & \text{for START\_S} < t < \text{END\_M} \end{cases}$$ — c

$$\frac{d}{dt}[Hct1] = \frac{(k'_{a,t1} + k''_{a,t1}[Cdc20]) \cdot ([Hct1]_T - [Hct1])}{J_{a,t1} + [Hct1]_T - [Hct1]} - \frac{V_{i,t1}[Hct1]}{J_{i,t1} + [Hct1]}$$

$$V_{i,t1} = k'_{i,t1} + k''_{i,t1}([Cln3]^* + \varepsilon_{i,t1,n2}[Cln2] + \varepsilon_{i,t1,b5}[Clb5] + \varepsilon_{i,t1,b2}[Clb2])$$

Equations for growth, DNA synthesis, budding and spindle formation

$$\frac{d}{dt}mass = \mu \cdot mass, \frac{d}{dt}[ORI] = k_{s,ori}([Clb5] + \varepsilon_{ori,b2}[Clb2]) - k_{d,ori}[ORI]$$ — d

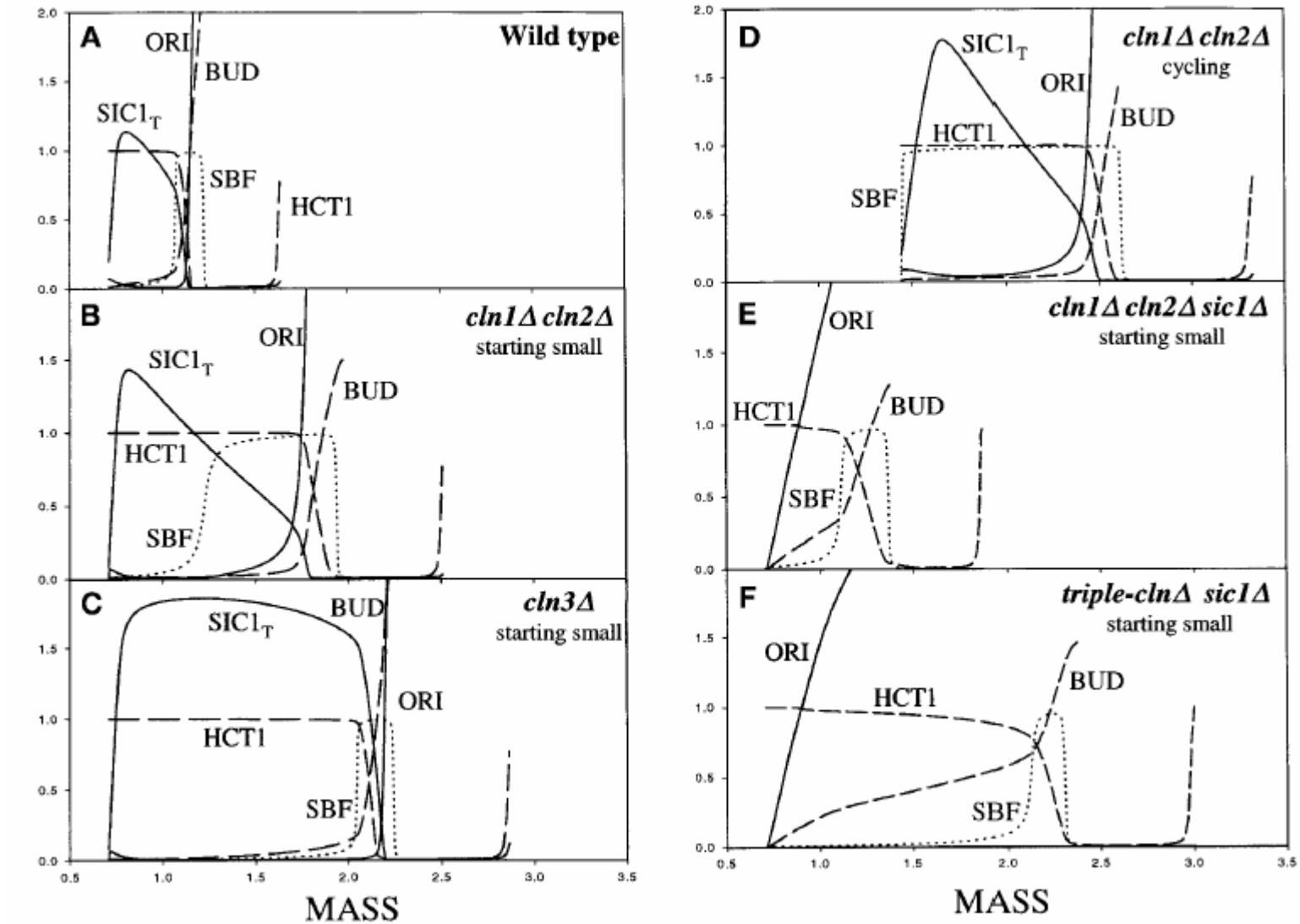
$$\frac{d}{dt}[BUD] = k_{s,bud}([Cln2] + [Cln3]^* + \varepsilon_{bud,b5}[Clb5]) - k_{d,bud}[BUD], \frac{d}{dt}[SPN] = k_{s,spn}\frac{[Clb2]}{J_{spn} + [Clb2]} - k_{d,spn}[SPN]$$

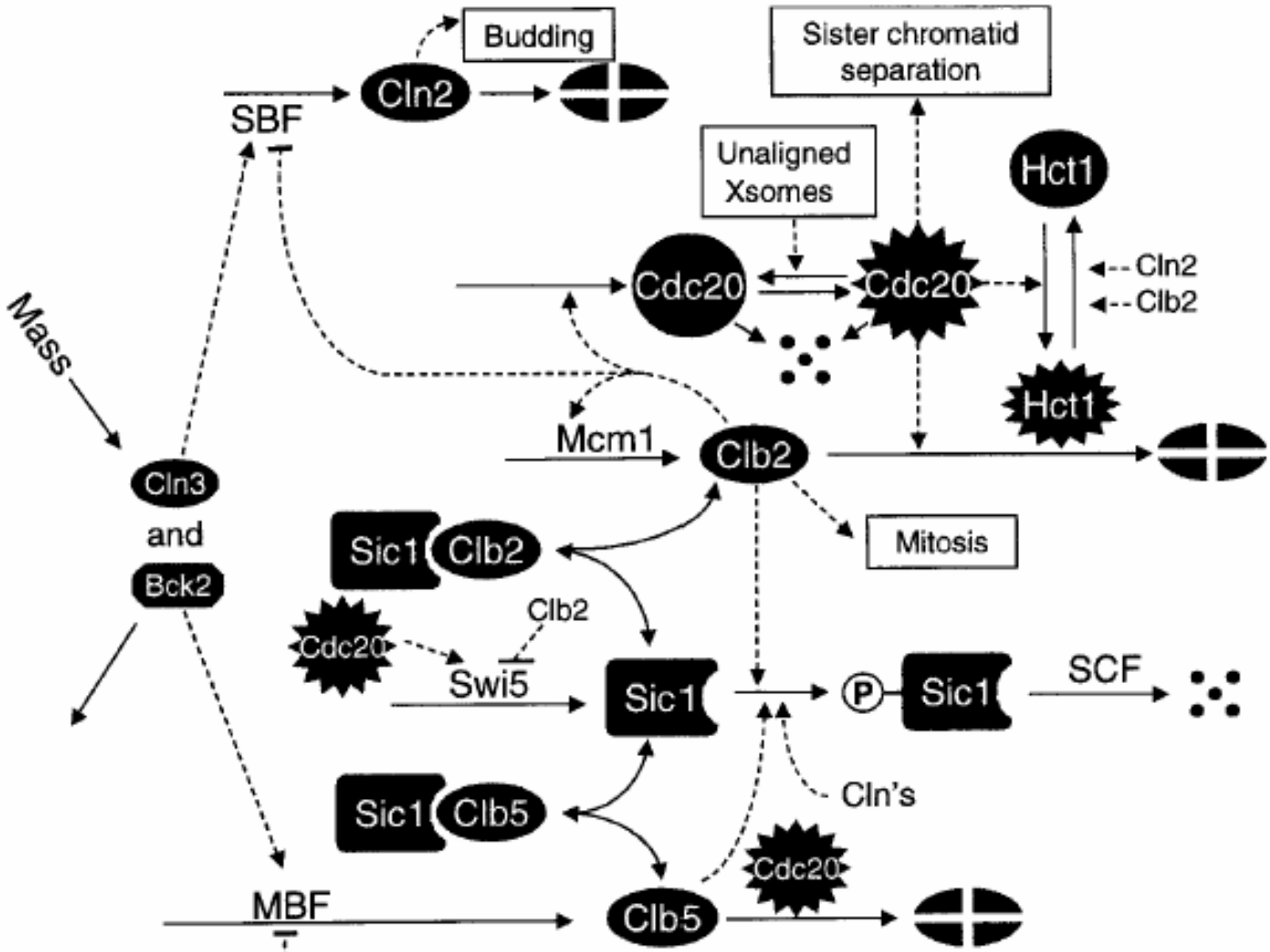
Equations governing transcription factors — e

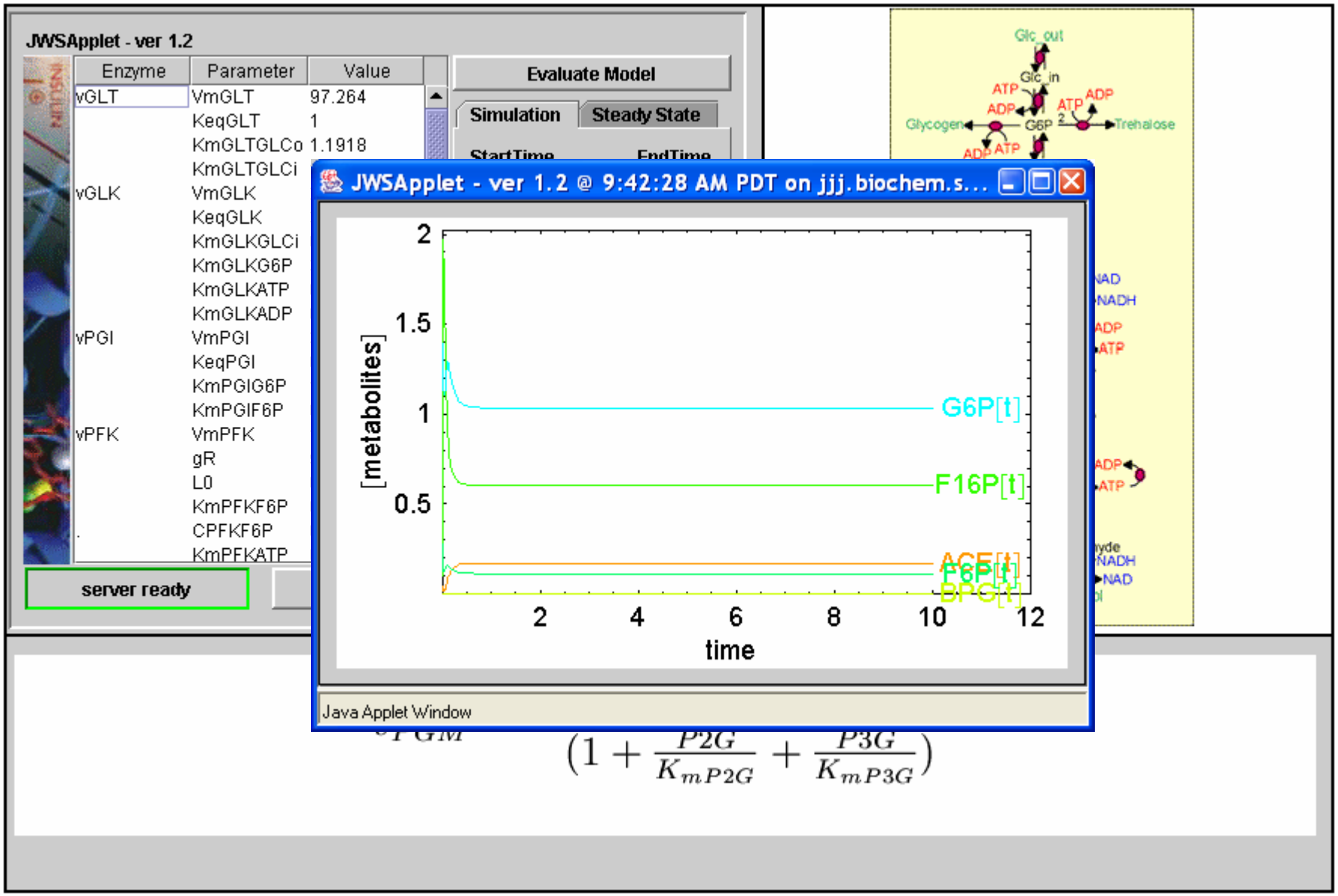
$$[SBF] = [MBF] = G(V_{a,sbf}, k'_{i,sbf} + k''_{i,sbf}[Clb2], J_{a,sbf}, J_{i,sbf}),\ V_{a,sbf} = k_{a,sbf}([Cln2] + \varepsilon_{sbf,n3}([Cln3]^* + [Bck2]) + \varepsilon_{sbf,b5}[Clb5]),$$

$$[Mcm1] = G(k_{a,mcm}[Clb2], k_{i,mcm}, J_{a,mcm}, J_{i,mcm}),\ [Swi5] = G(k_{a,swi}[Cdc20], k'_{i,swi} + k''_{i,swi}[Clb2], J_{a,swi}, J_{i,swi})$$

Symbols, V = rate functions, k = rate constant, J = Michaelis constant. Subscripts, s = synthesis, d = degradation, a = activation, i = inactivation, as = association, di = dissociation, T = total


A
Wild type
ORI
BUD
SIC1T
SBF
HCT1
B
cln1Δ cln2Δ
starting small
ORI
SIC1T
BUD
HCT1
SBF
C
cln3Δ
starting small
SIC1T
BUD
ORI
HCT1
SBF
D
cln1Δ cln2Δ
cycling
SIC1T
ORI
HCT1
BUD
SBF
E
cln1Δ cln2Δ sic1Δ
starting small
ORI
HCT1
BUD
SBF
F
triple-clnΔ sic1Δ
starting small
ORI
HCT1
BUD
SBF
MASS
MASS

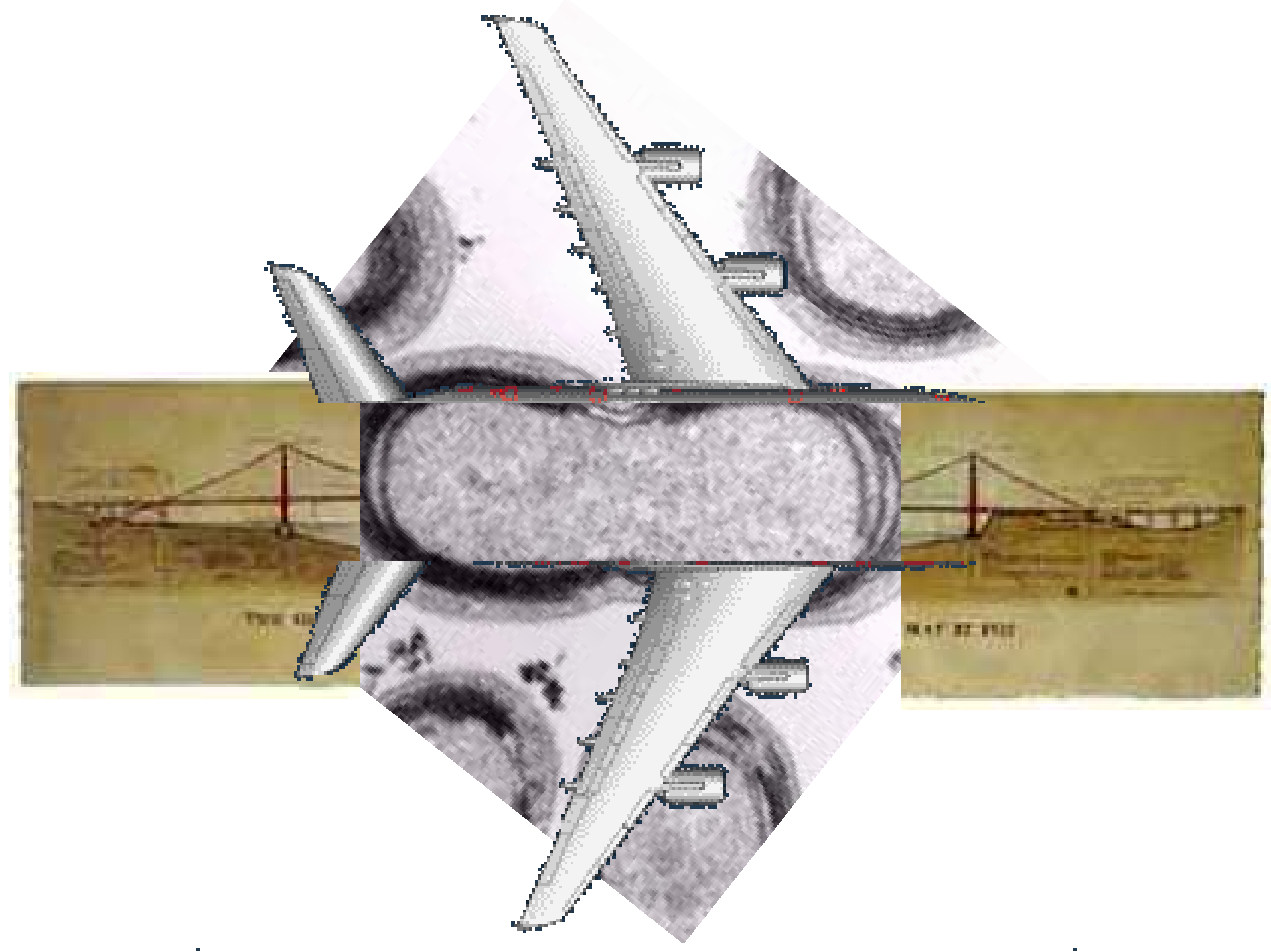

Budding
Cln2
SBF
Sister chromatid separation
Unaligned Xsomes
Hct1
Cdc20
Cdc20
Cln2
Clb2
Hct1
Mass
Mcm1
Clb2
Cln3
and
Bck2
Sic1
Clb2
Mitosis
Clb2
Cdc20
Swi5
Sic1
P
Sic1
SCF
Cln's
Sic1
Clb5
Cdc20
MBF
Clb5

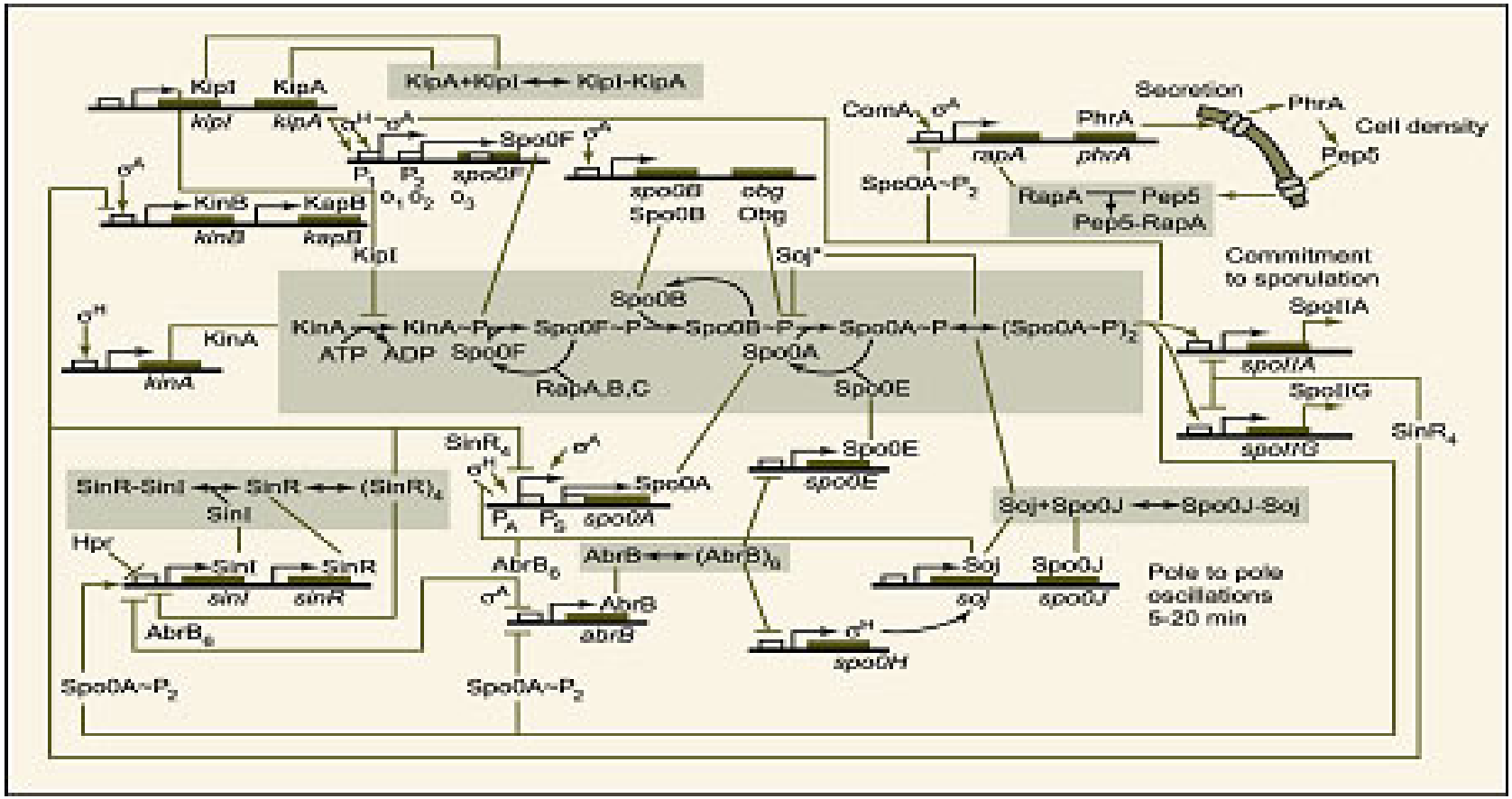


$$(1 + \frac{P2G}{K_{mP2G}} + \frac{P3G}{K_{mP3G}})$$

Qualitative  **Quantitative**

Not enough data





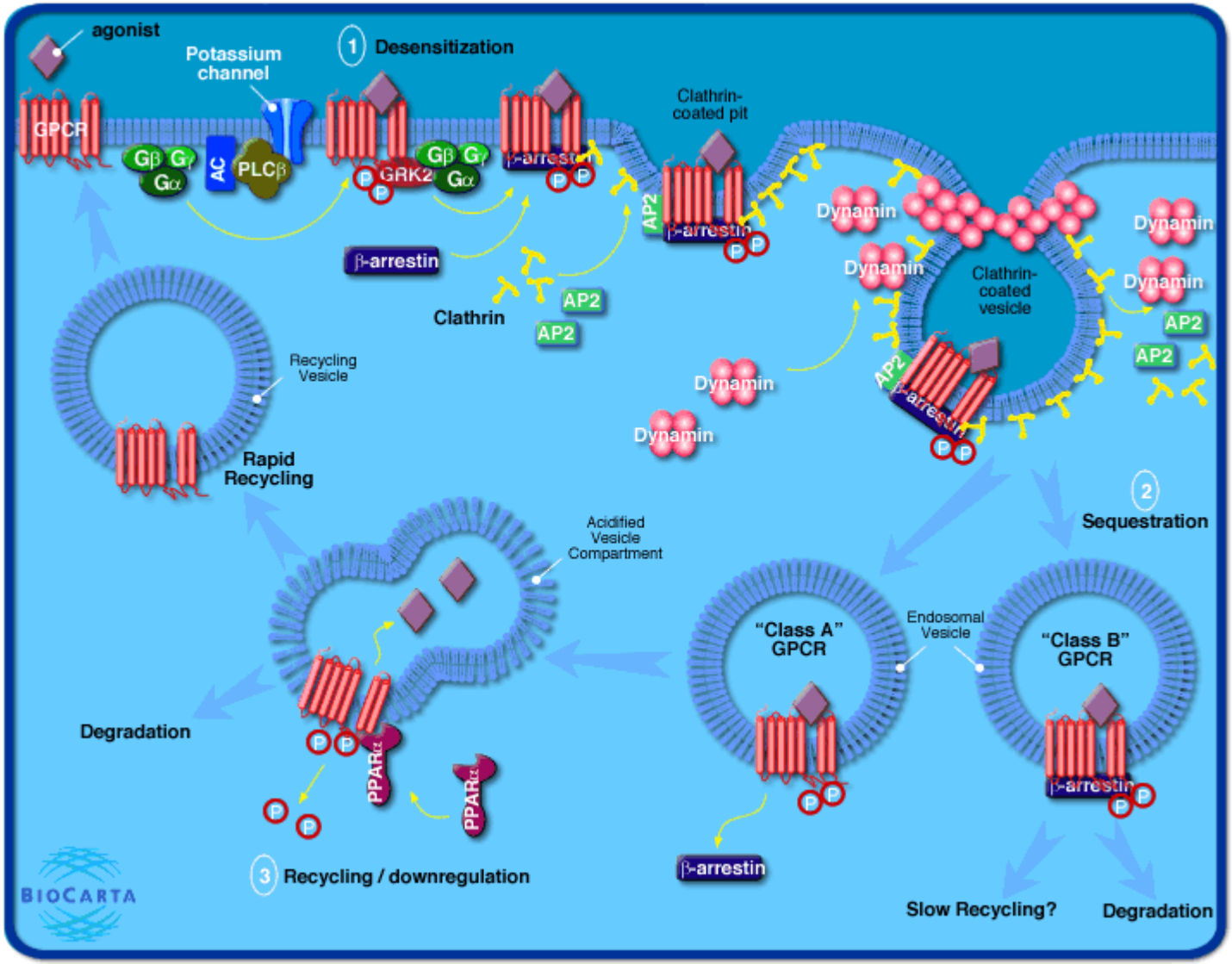
Bio-SPICE analysis of key switches in sporulation network
Overall sporulation network: B. subtilis - common across mutants
Source: Bio-SPICE projects at LBNL (PI: Adam Arkin)

Qualitative  **Quantitative**

Not enough data

Can’t do “operating logics”

ß-arrestins in GPCR Desensitization



Qualitative  **Quantitative**

Not enough data

Can’t do “operating logics”

Not expressive enough

Parts
Processes
Dynamics
Operating Logic

Not Just for Messages

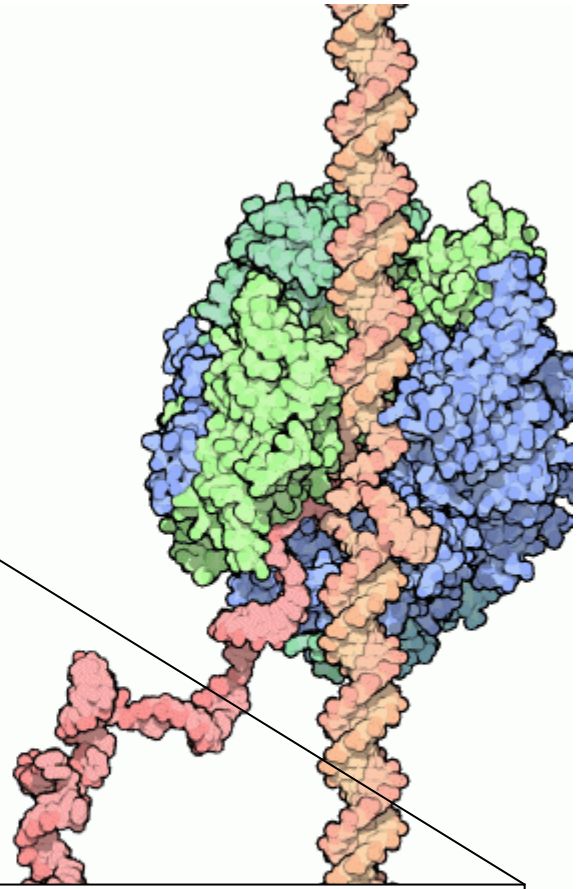
RNA is a versatile molecule. In its most familiar role, RNA acts as an intermediary, carrying genetic information from the DNA to the machinery of protein synthesis. RNA also plays more active roles, performing many of the catalytic and recognition functions normally reserved for proteins. In fact, most of the RNA in cells is found in ribosomes--our protein-synthesizing machines--and the transfer RNA molecules used to add each new amino acid to growing proteins. In addition, countless small RNA molecules are involved in regulating, processing and disposing of the constant traffic of messenger RNA. The enzyme RNA polymerase carries the weighty responsibility of creating all of these different RNA molecules.

The RNA Factory

RNA polymerase is a huge factory with many moving parts. The one shown here, from PDB entry 1i6h, is from yeast cells. It is composed of a dozen different proteins. Together, they form a machine that surrounds DNA strands, unwinds them, and builds an RNA strand based on the information held inside the DNA. Once the enzyme gets started, RNA polymerase marches confidently along the DNA copying RNA strands thousands of nucleotides long.

Accuracy

As you might expect, RNA polymerase needs to be accurate in its copying of genetic information. To improve its accuracy,
is designed to be able
tends to hover around
to remove them. This
removed, but this is a
about once per RNA



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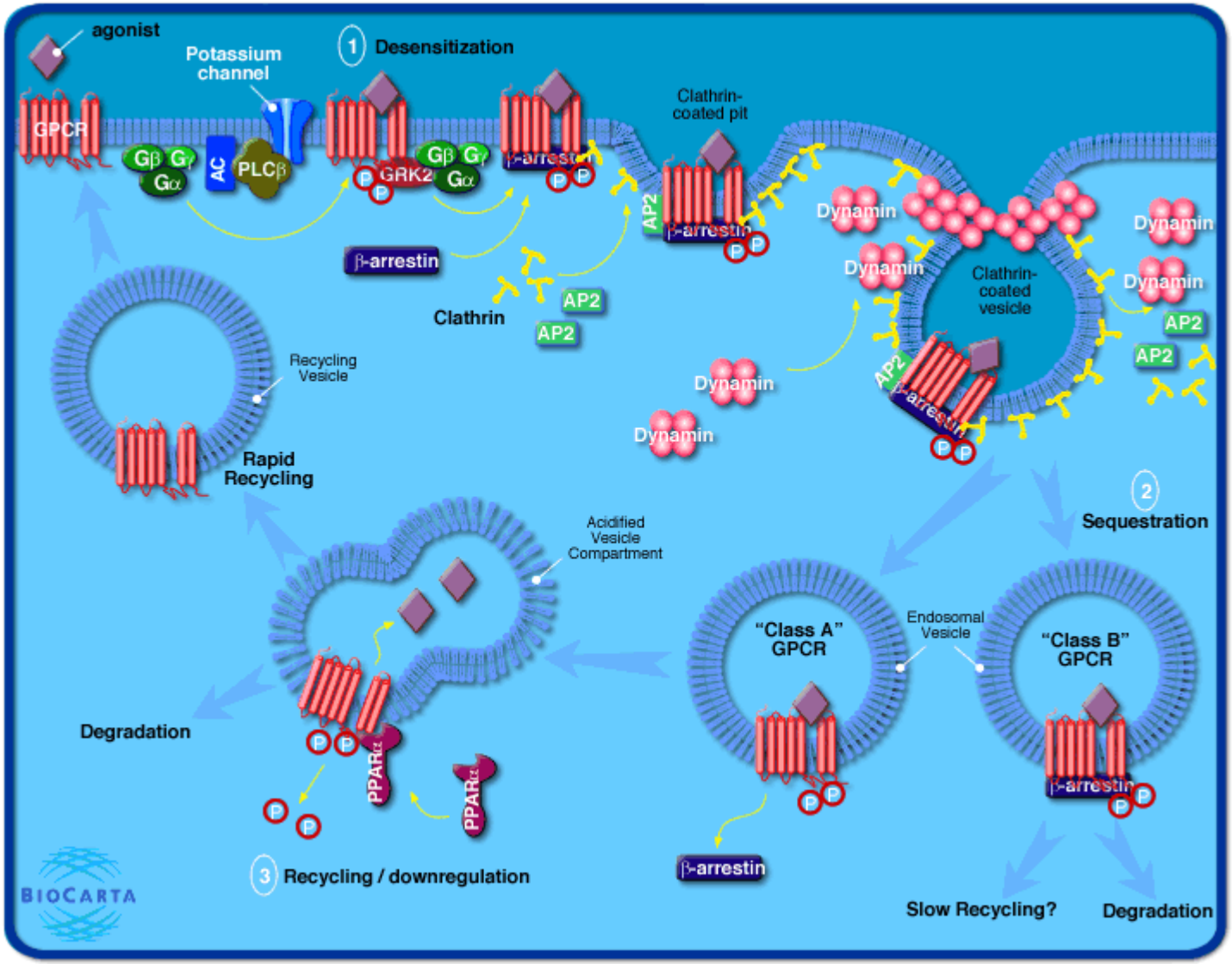
ß-arrestins in GPCR Desensitization

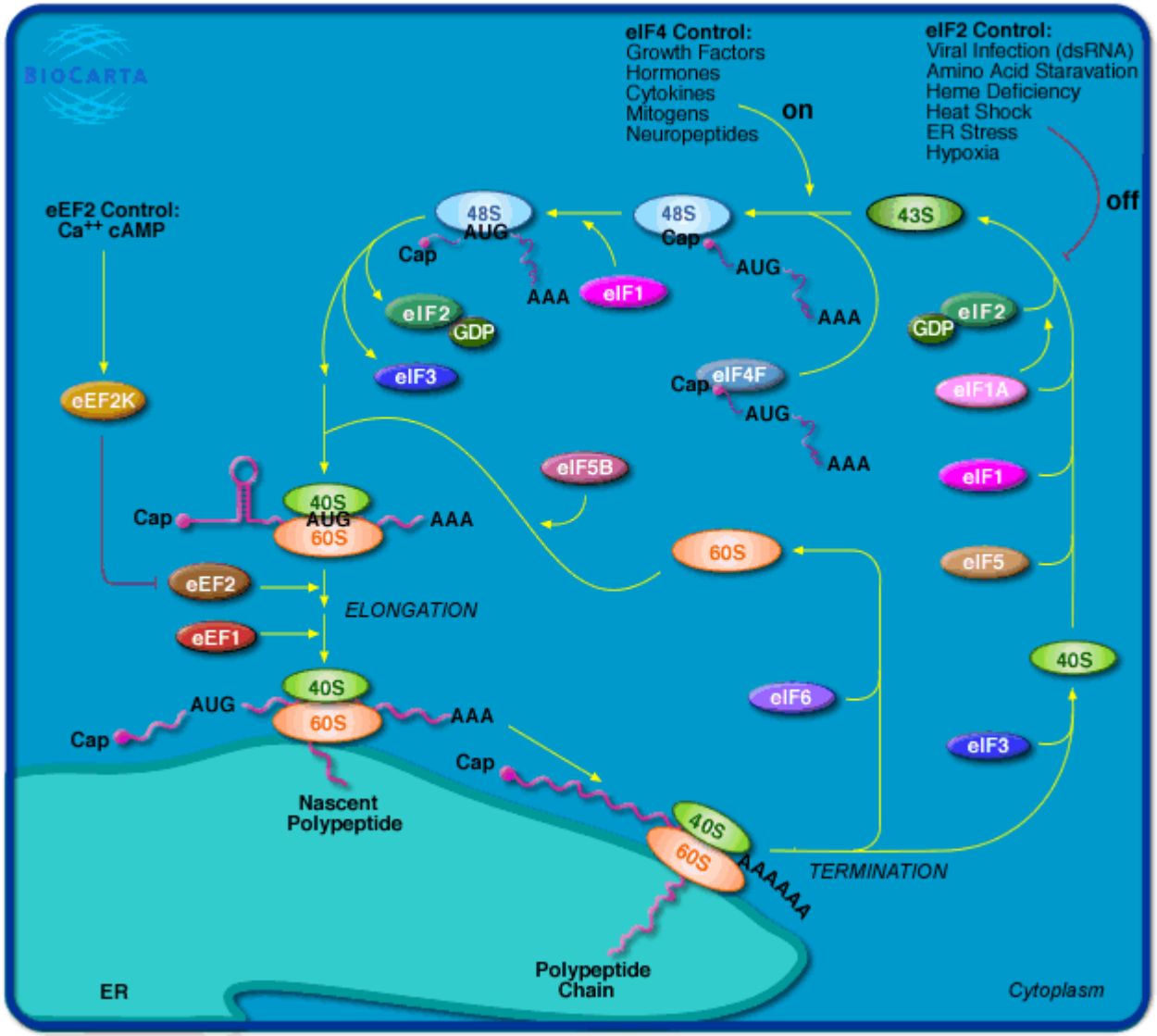


www.biocarta.com

C

- Ca++/ Calmodulin-dependent Protein Kinase Activation [H] [M]
- Cadmium induces DNA synthesis and proliferation in macrophages [H] [M]
- Calcium Signaling by HBx of Hepatitis B virus [H] [M]
- Cardiac Protection Against ROS [H]
- CARM1 and Regulation of the Estrogen Receptor [H]
- Caspase Cascade in Apoptosis [H] [M]
- Catabolic pathway for asparagine and asparate
- Catabolic pathways for alanine, glycine, serine, cysteine, tryptophan, and threonine
- Catabolic Pathways for Arginine , Histidine, Glutamate, Glutamine, and Proline [H] [M]
- Catabolic Pathways for Methionine, Isoleucine, Threonine and Valine [H] [M]
- CBL mediated ligand-induced downregulation of EGF receptors [H] [M]
- CCR3 signaling in Eosinophils [H] [M]
- CD40L Signaling Pathway [H] [M]
- cdc25 and chk1 Regulatory Pathway in response to DNA damage [H] [M]
- CDK Regulation of DNA Replication [H] [M]
- Cell Cycle: G1/S Check Point [H] [M]
- Cell Cycle: G2/M Checkpoint [H] [M]
- Cell to Cell Adhesion Signaling [H] [M]
- Cells and Molecules involved in local acute inflammatory response [H]
- Ceramide Signaling Pathway [H] [M]
- Chaperones modulate interferon Signaling Pathway [H]
- ChREBP regulation by carbohydrates and cAMP [H] [M]
- Chromatin Remodeling by hSWI/SNF ATP-dependent Complexes [H] [M]
- Circadian Rhythms [H] [M]
- Classical Complement Pathway [H] [M]
- Comparison of Beta oxidation in mitochondria and peroxisomes and glyoxysomes
- Complement Pathway [H] [M]
- Control of Gene Expression by Vitamin D Receptor [H] [M]
- Control of skeletal myogenesis by HDAC & calcium/calmodulin-dependent kinase (CaMK) [H] [M]
- Corticosteroids and cardioprotection [H] [M]
- CTCF: First Multivalent Nuclear Factor [H] [M]
- CTL mediated immune response against target cells [H] [M]
- CXCR4 Signaling Pathway [H] [M]
- Cyclin E Destruction Pathway [H] [M]
- Cycling of Ran in nucleocytoplasmic transport [H] [M]
- Cyclins and Cell Cycle Regulation [H] [M]
- Cystic fibrosis transmembrane conductance regulator and beta 2 adrenergic receptor pathway [H] [M]
- Cytokine Network [H] [M]
- Cytokines and Inflammatory Response [H] [M]

Eukaryotic protein translation



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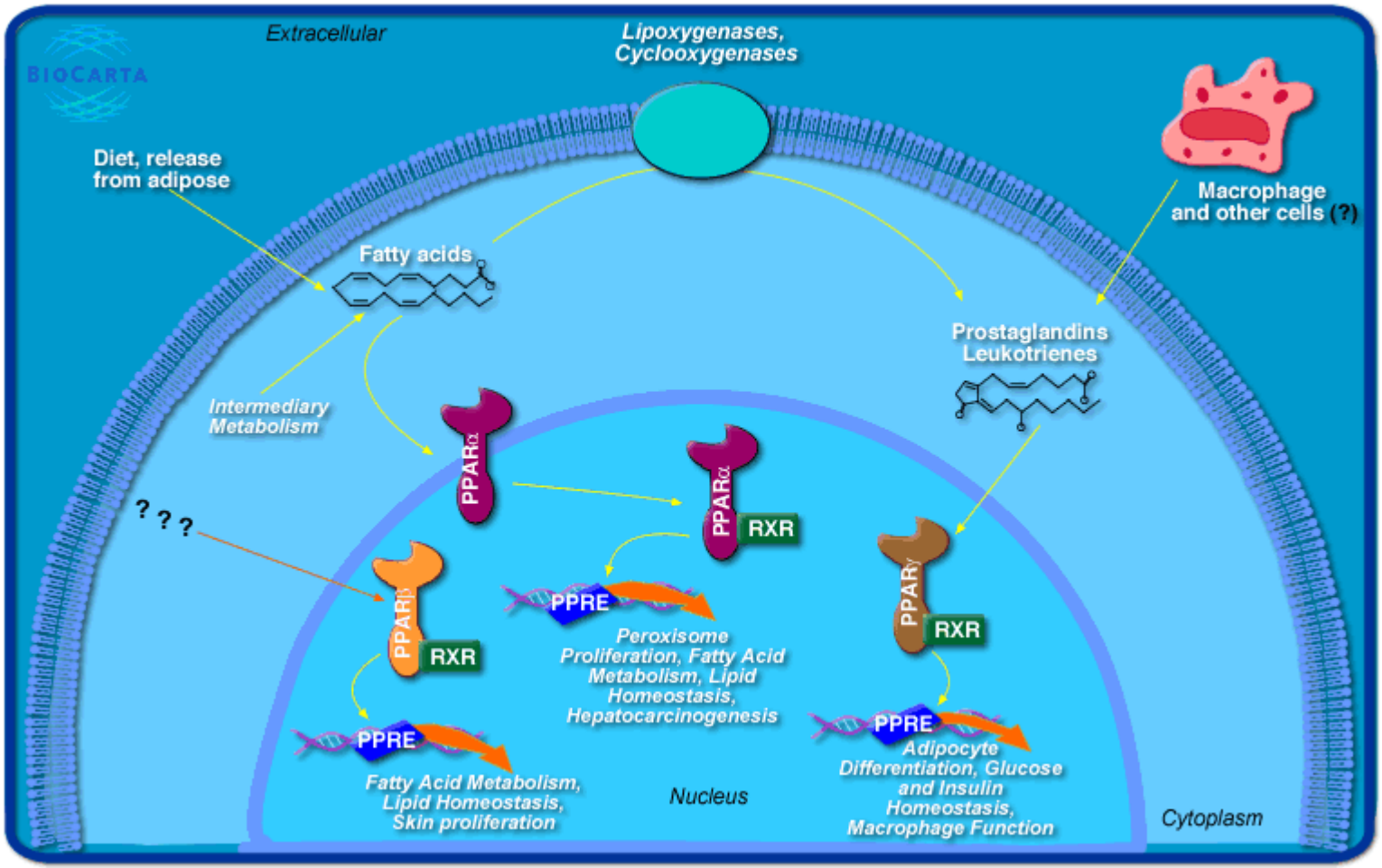
Action of PPARa, PPARb(d) and PPARg and effects on gene expression



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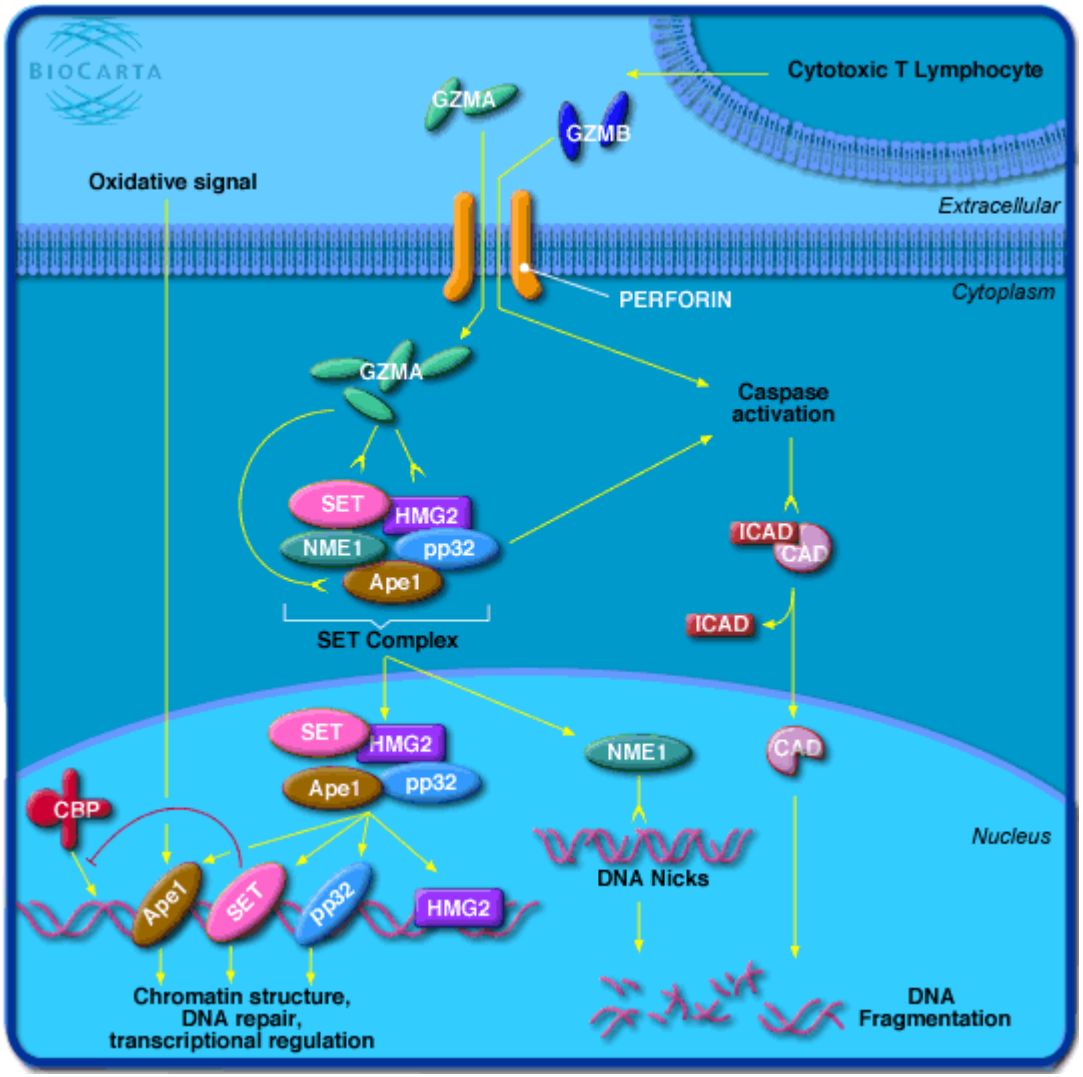
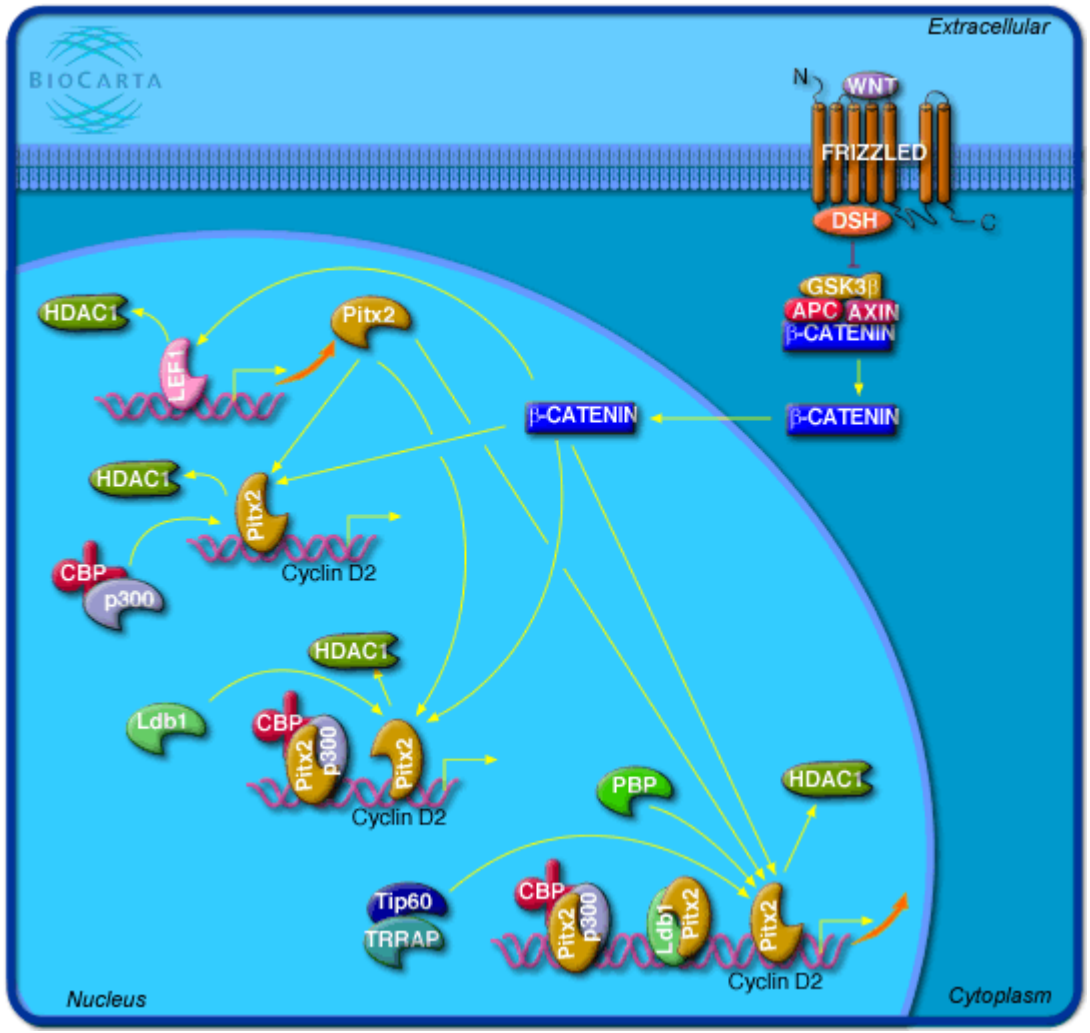
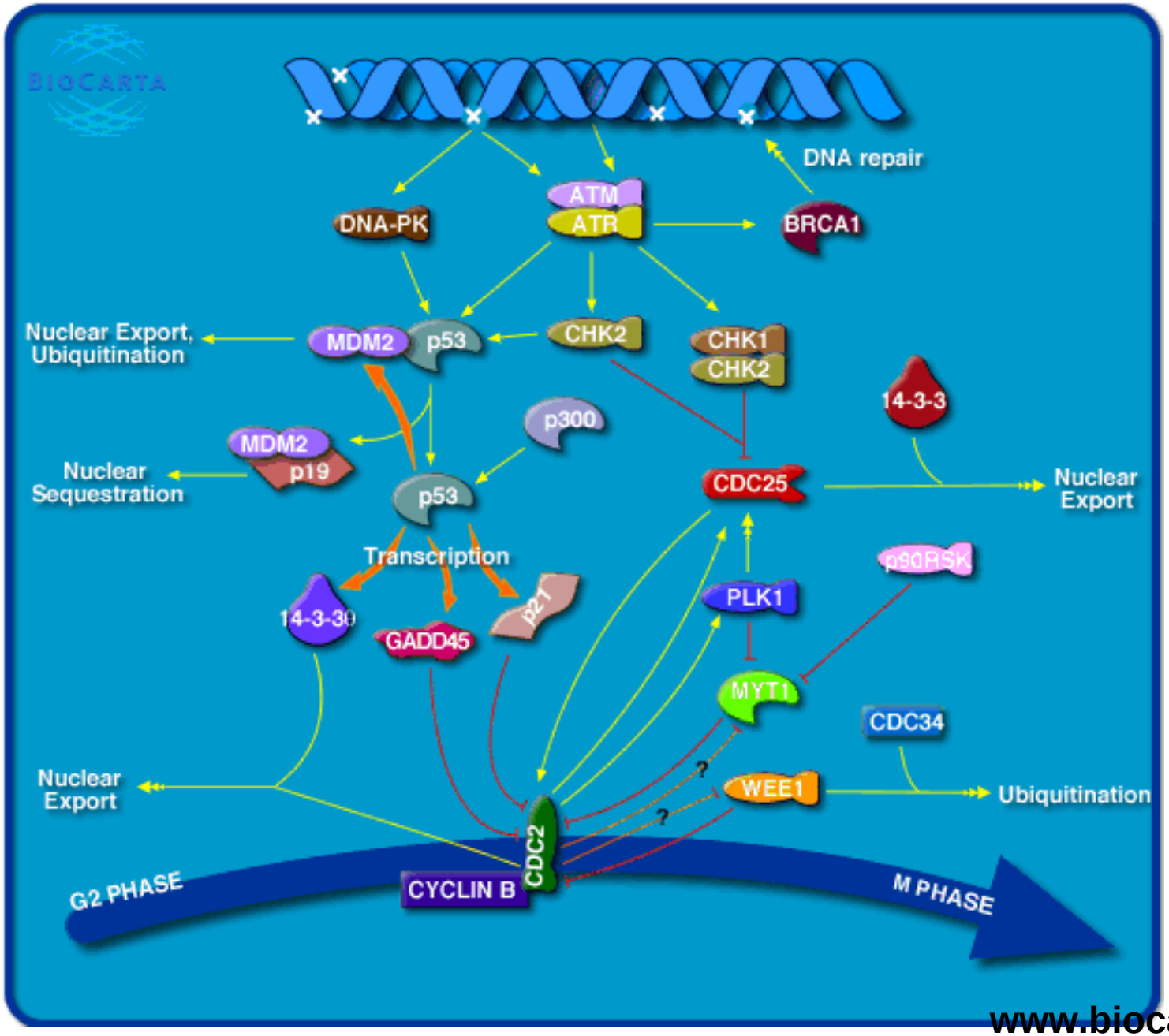
Granzyme A mediated Apoptosis Pathway



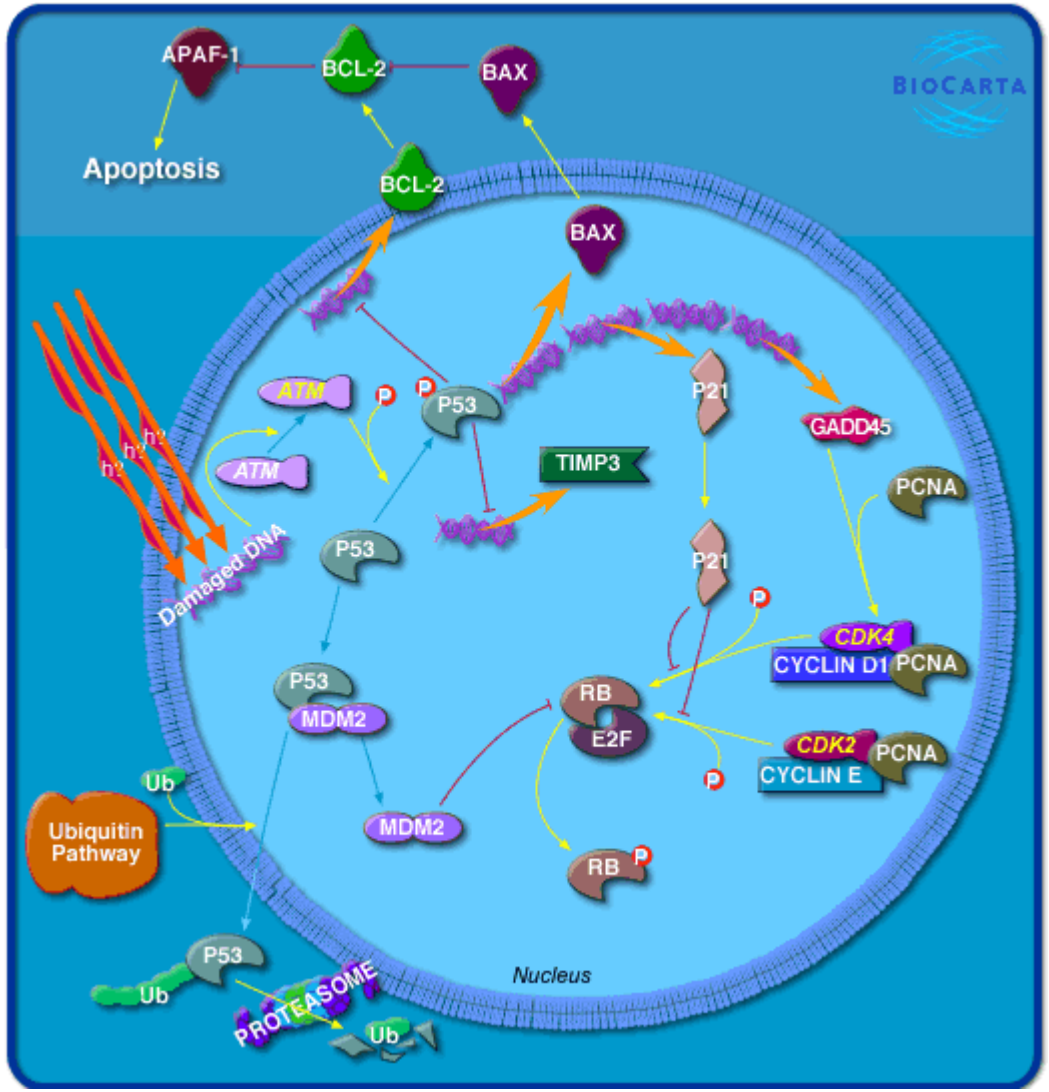
Multi-step Regulation of Transcription by Pitx2



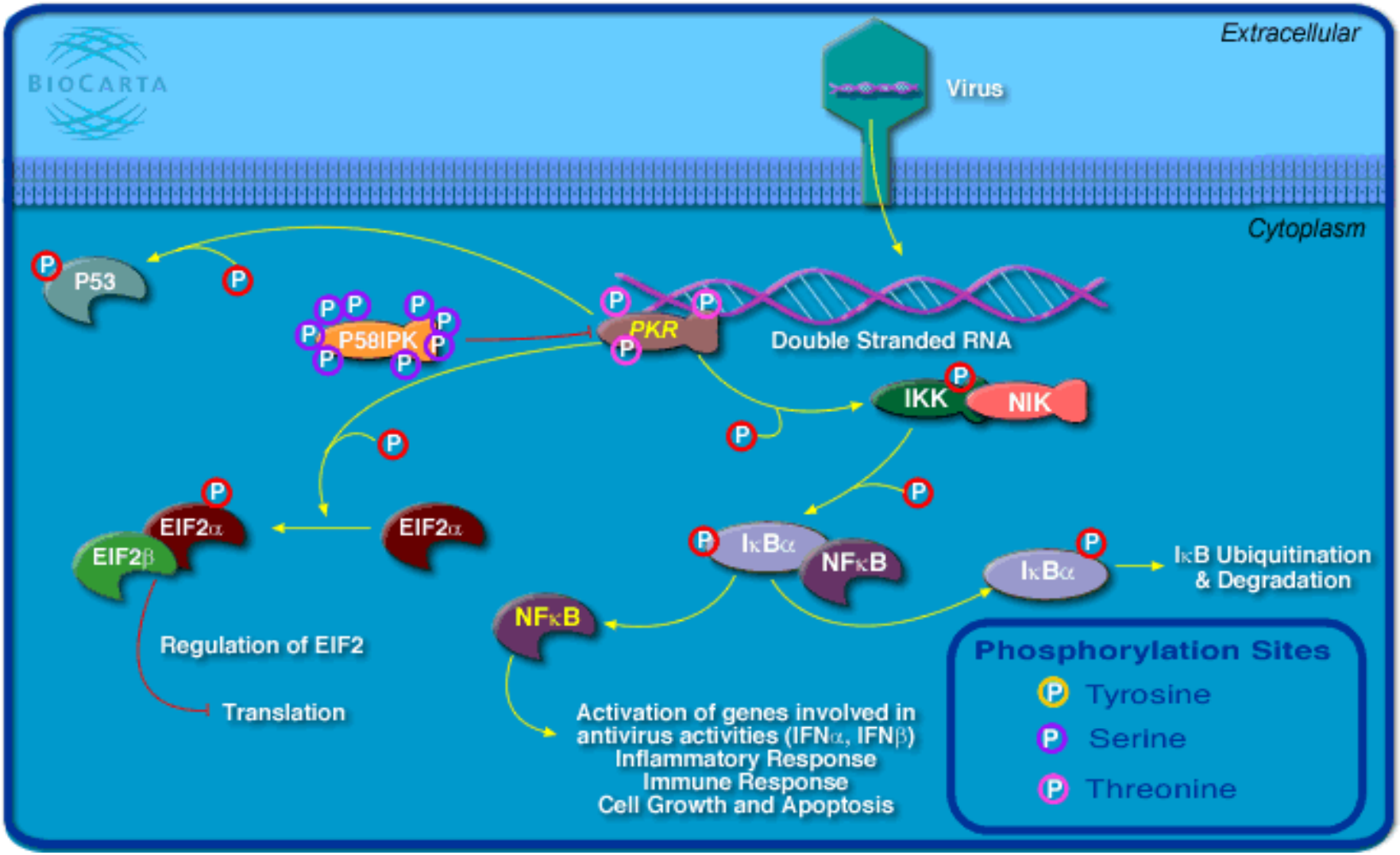
Cell Cycle: G2/M Checkpoint

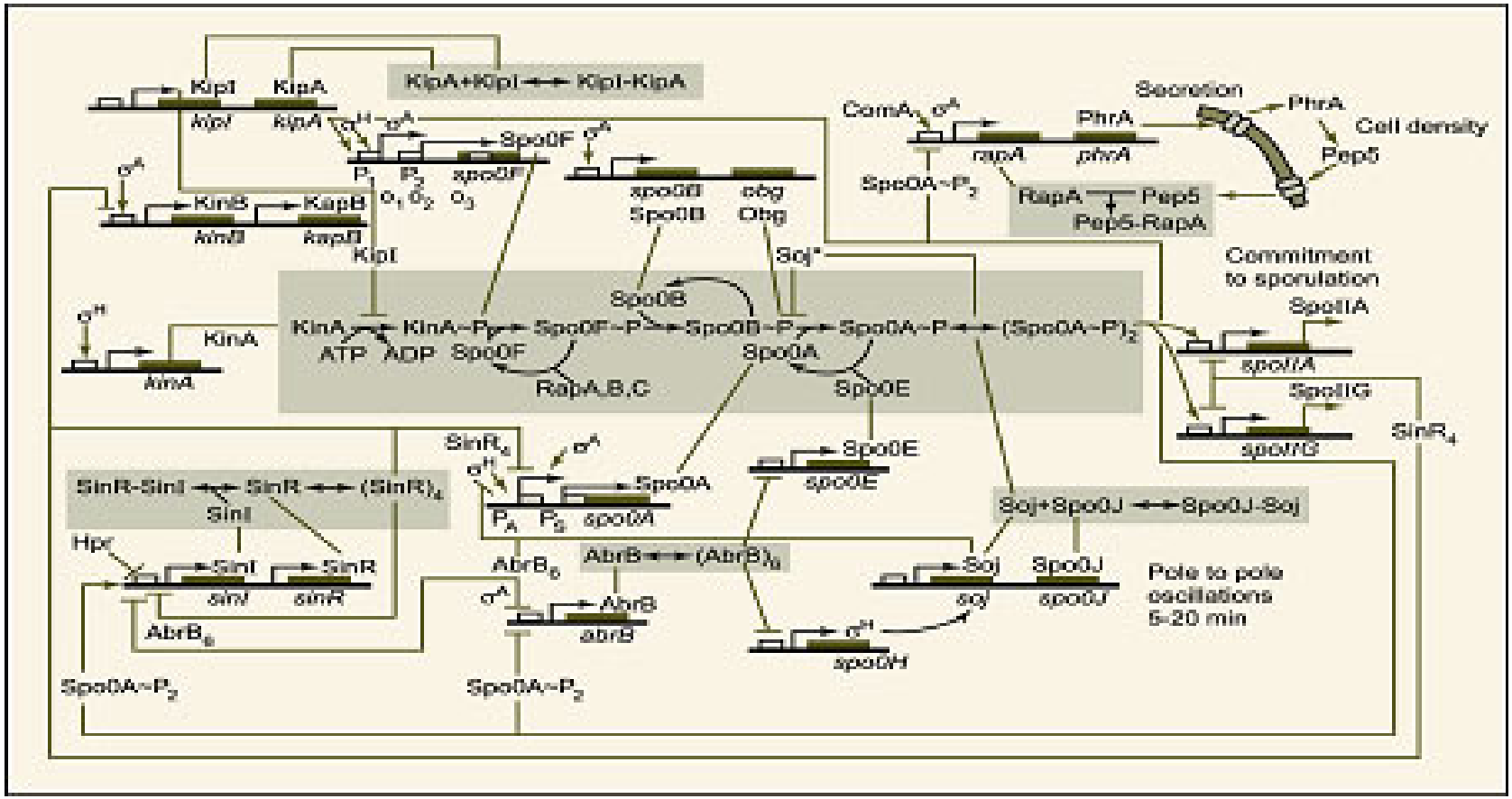


p53 Signaling Pathway



Double Stranded RNA Induced Gene Expression





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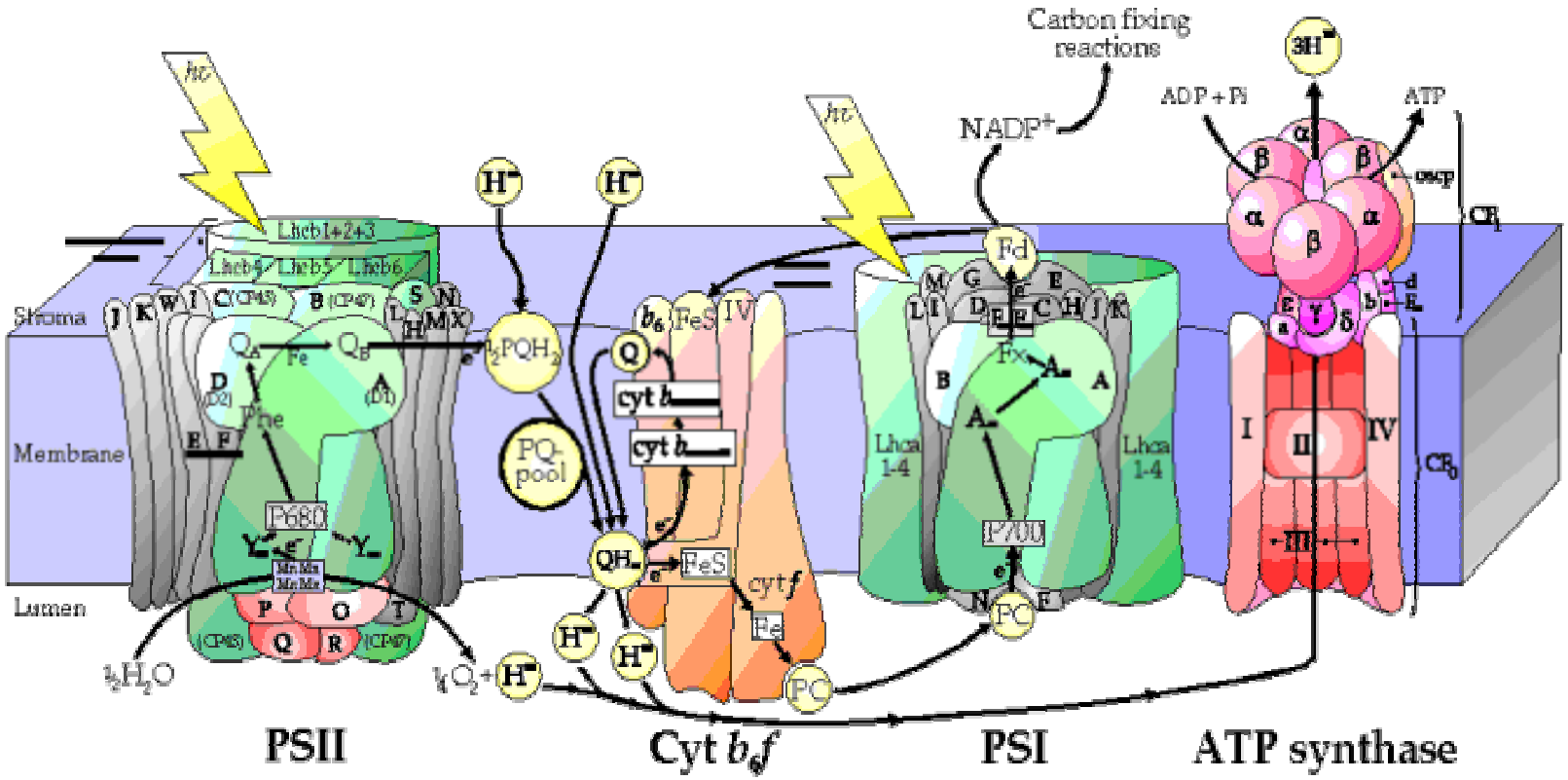
Photosynthesis (light reactions)



PhotoSynthesis (light reactions)

http://www.bio.ic.ac.uk/research/barber/photosystemII.html

How Lisp Will Save the World

Biological models are complex webs of parts, processes, dynamics, and operating logics.

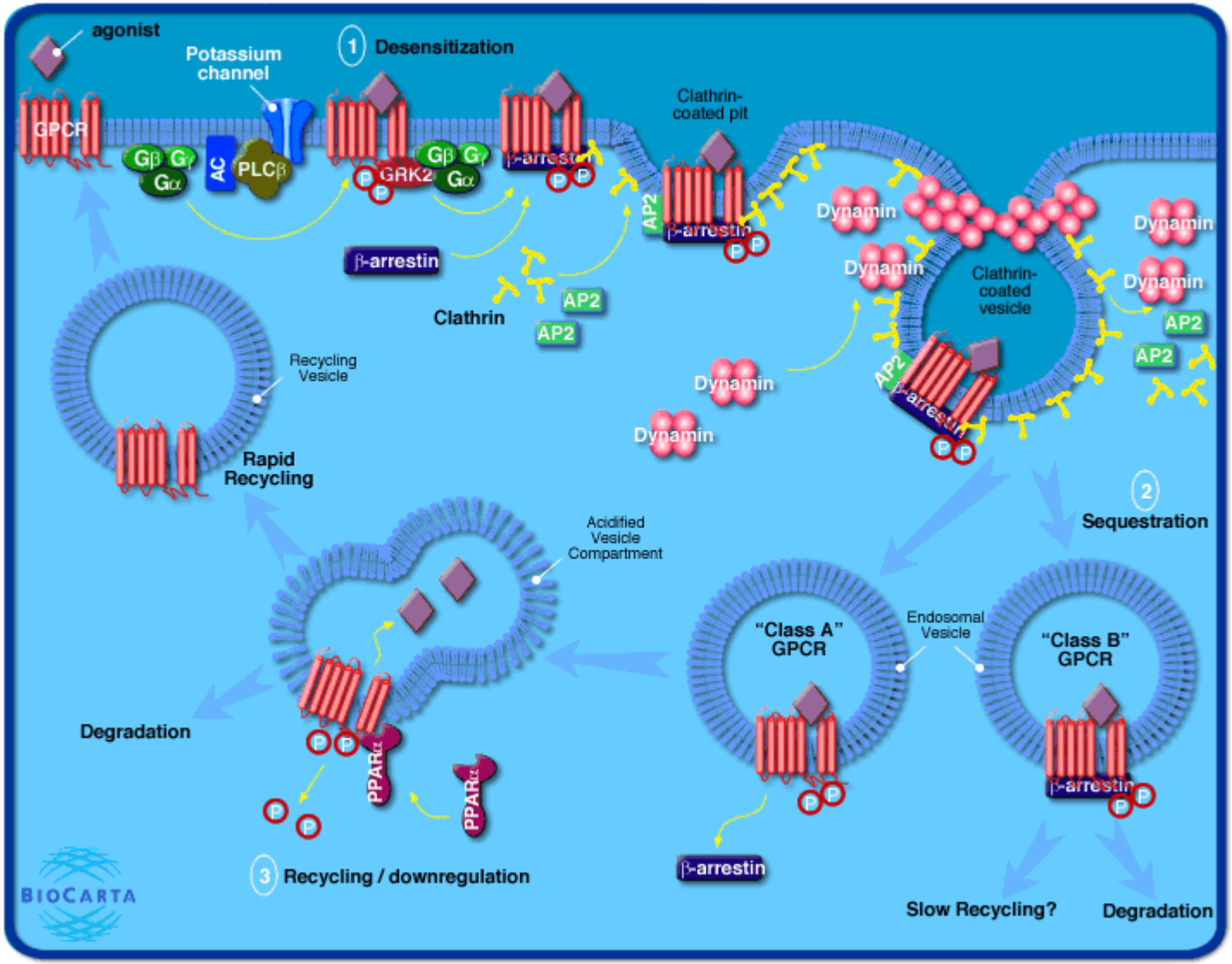
How Lisp Will Save the World

Biological models are complex webs of parts, processes, dynamics, and operating logics.

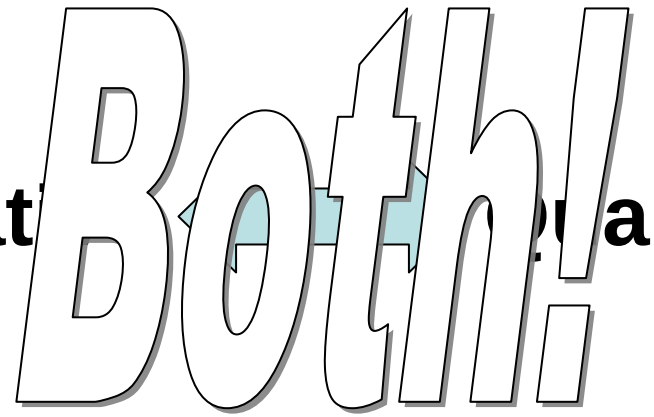
The expressions in these models range over both qualitative and quantitative value spaces.

Prochlorococcus

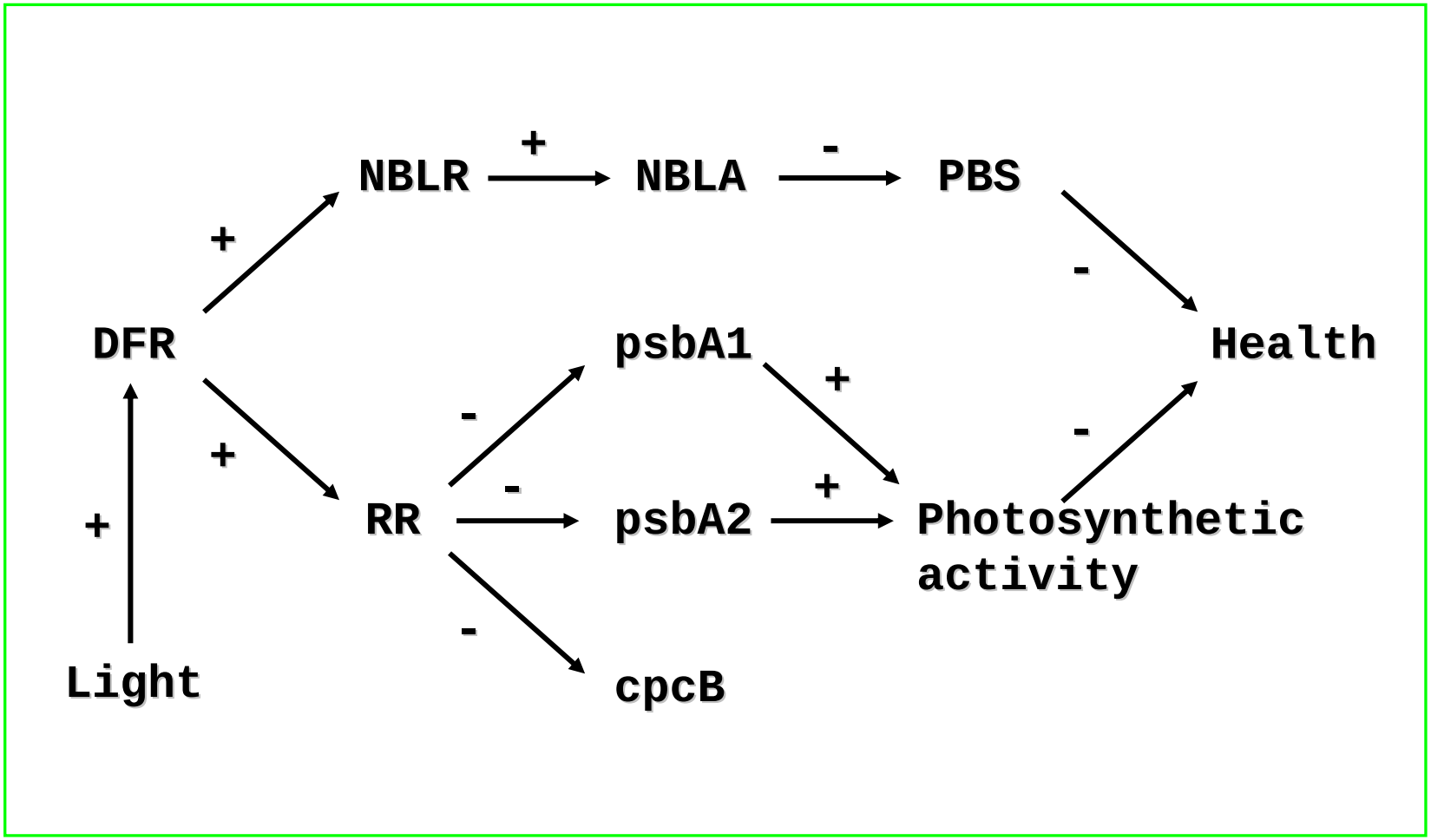
ß-arrestins in GPCR Desensitization



Qualitat **antitative**

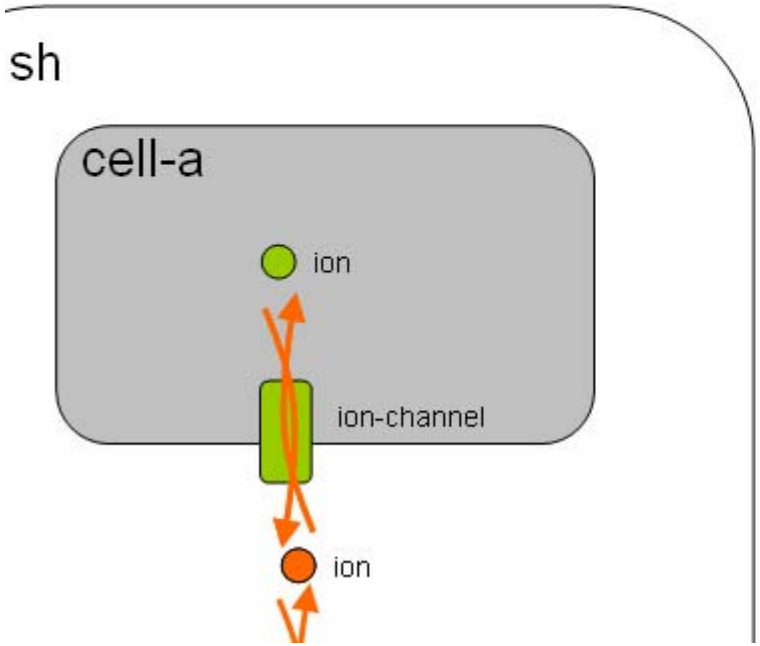


Causal/Regulatory Model



Shrager, et al. (2002)

ion-channel example:

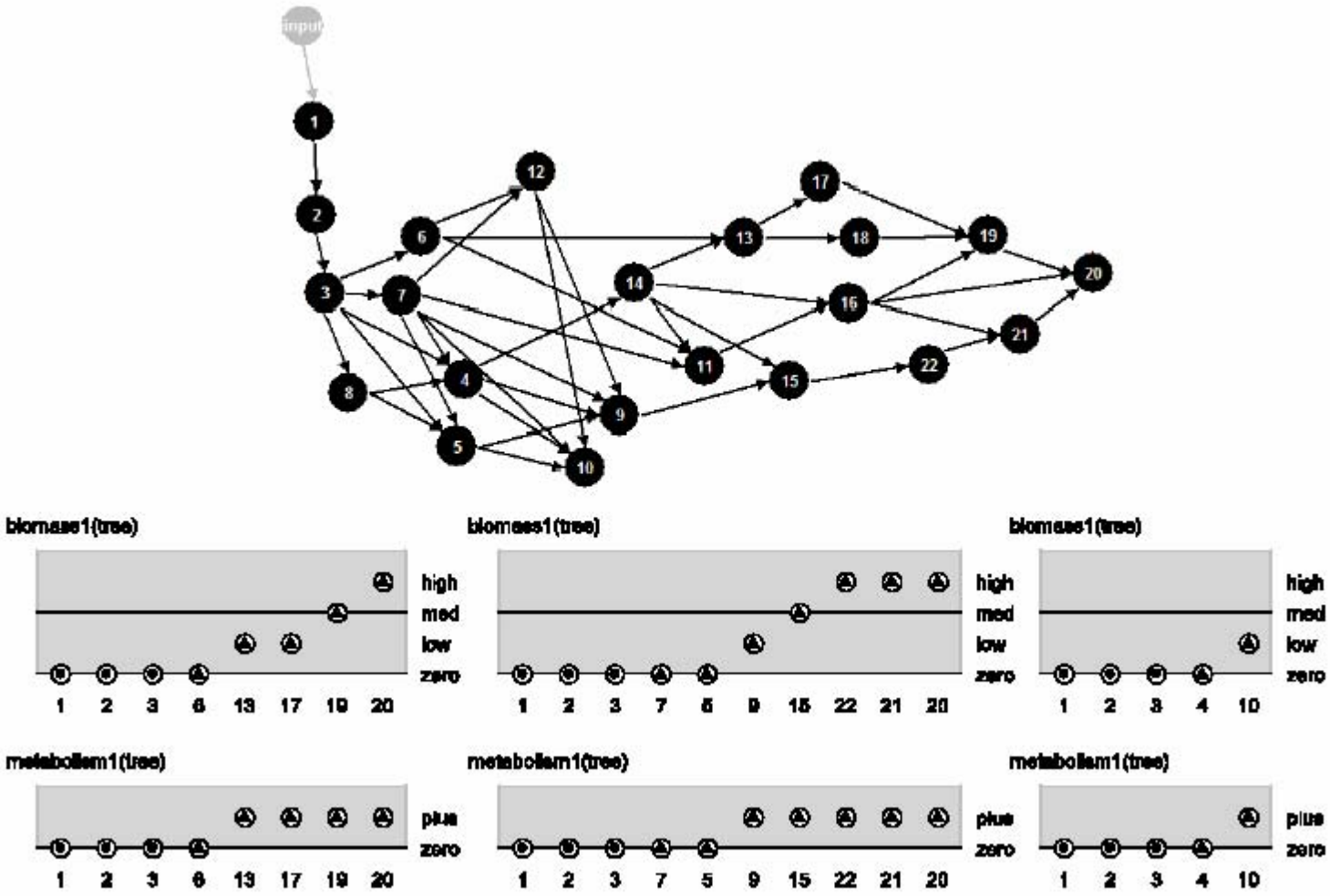



```
B-USER 20 > cell-a.membrane.(contains ion-channel)
(new) ion-channel.(in cell-a.membrane) :#= [reactant ion-c
ion-channel.(in cell-a.membrane) :#= [reactant ion-channel

B-USER 21 > cell-a.inner.(contains ion)
(new) ion.(in cell-a.inner) :#= [reactant ion cell-a.inner
(new) ion.(in dish) :#= [reactant ion dish]
(new) transport-rxn.rev.1.(in cell-a.membrane) :#= [reacti
(new) transport-rxn.fwd.1.(in cell-a.membrane) :#= [reacti
ion.(in cell-a.inner) :#= [reactant ion cell-a.inner]

B-USER 22 > cell-b.membrane.(contains ion-channel)
(new) ion-channel.(in cell-b.membrane) :#= [reactant ion-c
(new) ion.(in cell-b.inner) :#= [reactant ion cell-b.inner
(new) transport-rxn.fwd.1.(in cell-b.membrane) :#= [reacti
(new) transport-rxn.rev.1.(in cell-b.membrane) :#= [reacti
ion-channel.(in cell-b.membrane) :#= [reactant ion-channel
```

“little b”, aneil mallavarapu



http://qr05.tugraz.at/files/p18.pdf

model Photo_Reg;

variables $light, mRNA, photo\_protein, ROS, redox, transcriptio$
observables $light, mRNA$;
initials $mRNA = 0.253, photo\_protein = 0.836, ROS = 0.059, re$

process photosynthesis;
  equations $d[redox, t, 1] = 0.0155 * light * photo\_protein$;
            $d[ros, t, 1] = 0.019 * light * photo\_protein$;

process photo_translation;
  equations $d[photo\_protein, t, 1] = 7.539 * mRNA$;

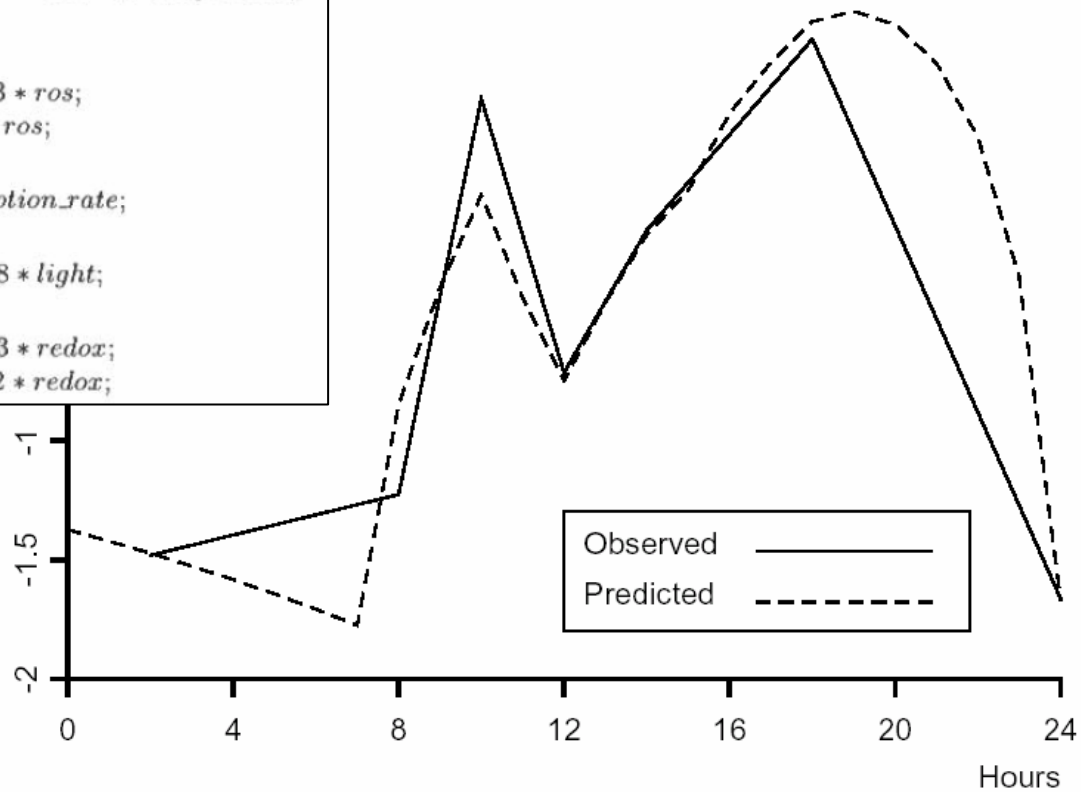
process automatic_degradation1;
  conditions $photo\_protein > 0$;
  equations $d[photo\_protein, t, 1] = -1 * 1.905 * photo\_protein$;

process controlled_degradation1;
  conditions $redox > 0, ros > 0$;
  equations $d[redox, t, 1] = -1 * 0.0003 * ros$;
            $d[ros, t, 1] = -1 * 0.0003 * ros$;

process mRNA_transcription;
  equations $d[mRNA, t, 1] = transcription\_rate$;

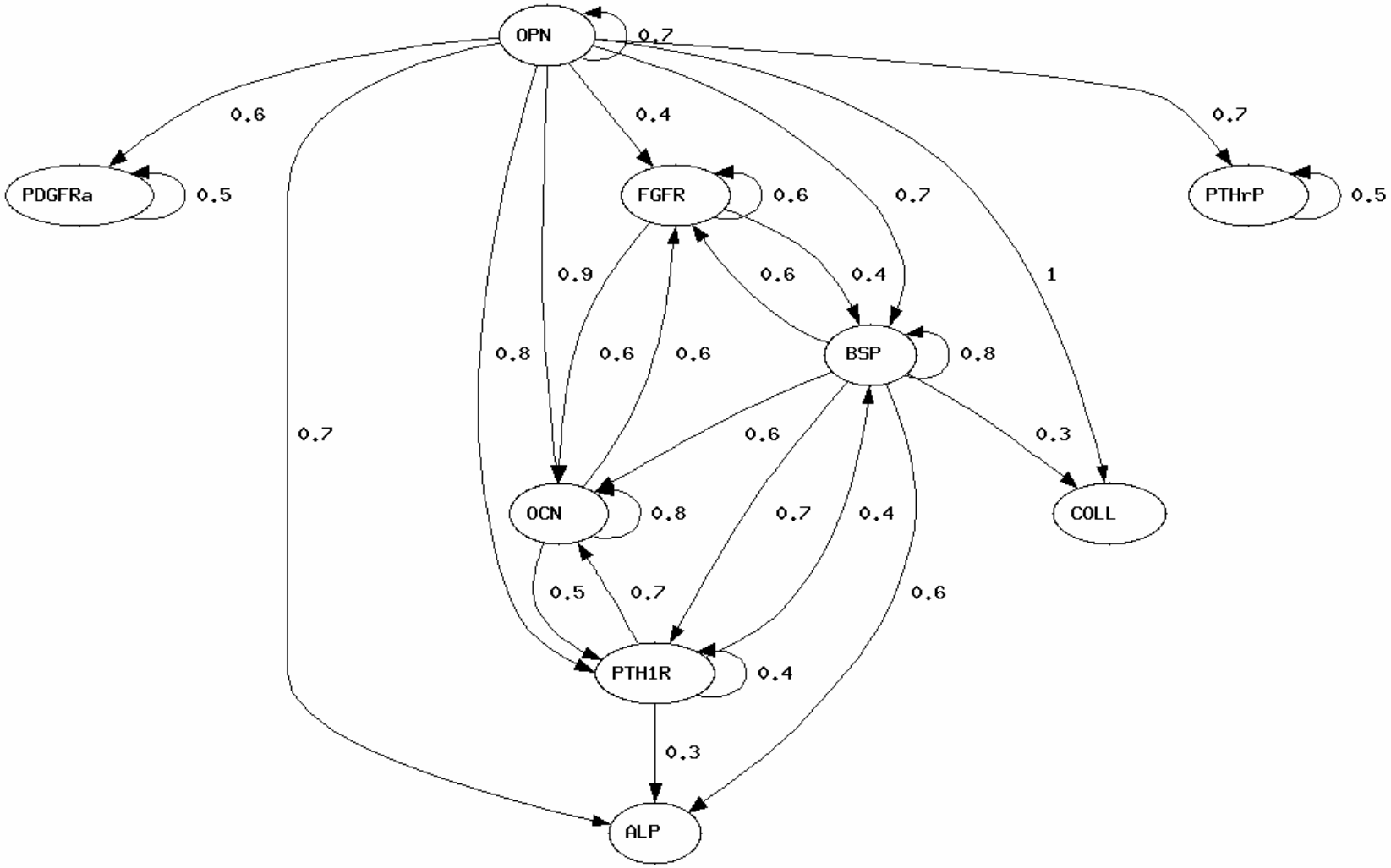
process regulate_one_1;
  equations $transcription\_rate = 0.938 * light$;

process regulate_two_2;
  equations $transcription\_rate = 1.203 * redox$;
            $d[redox, t, 1] = -1 * 0.0002 * redox$;



Predicted and observed levels of average gene expression over a 24-hour period.

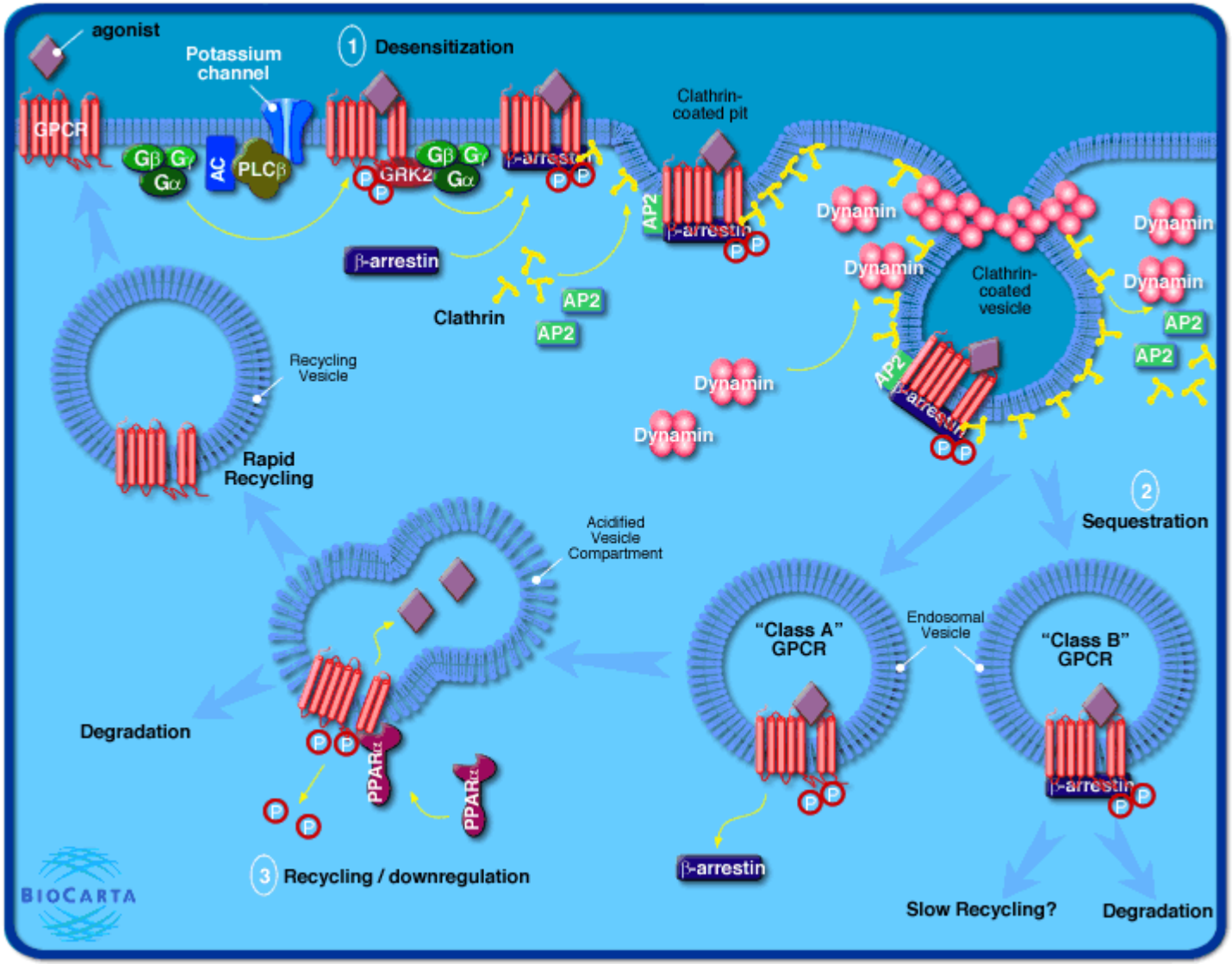
<11>> (solve-constraints "test.cons")



::

(solve-constraints "test.cons") [Enter]

ß-arrestins in GPCR Desensitization



How Lisp Will Save the World

Biological models are complex webs of parts, processes, dynamics, and operating logics.

The expressions in these models range over both qualitative and quantitative value spaces.

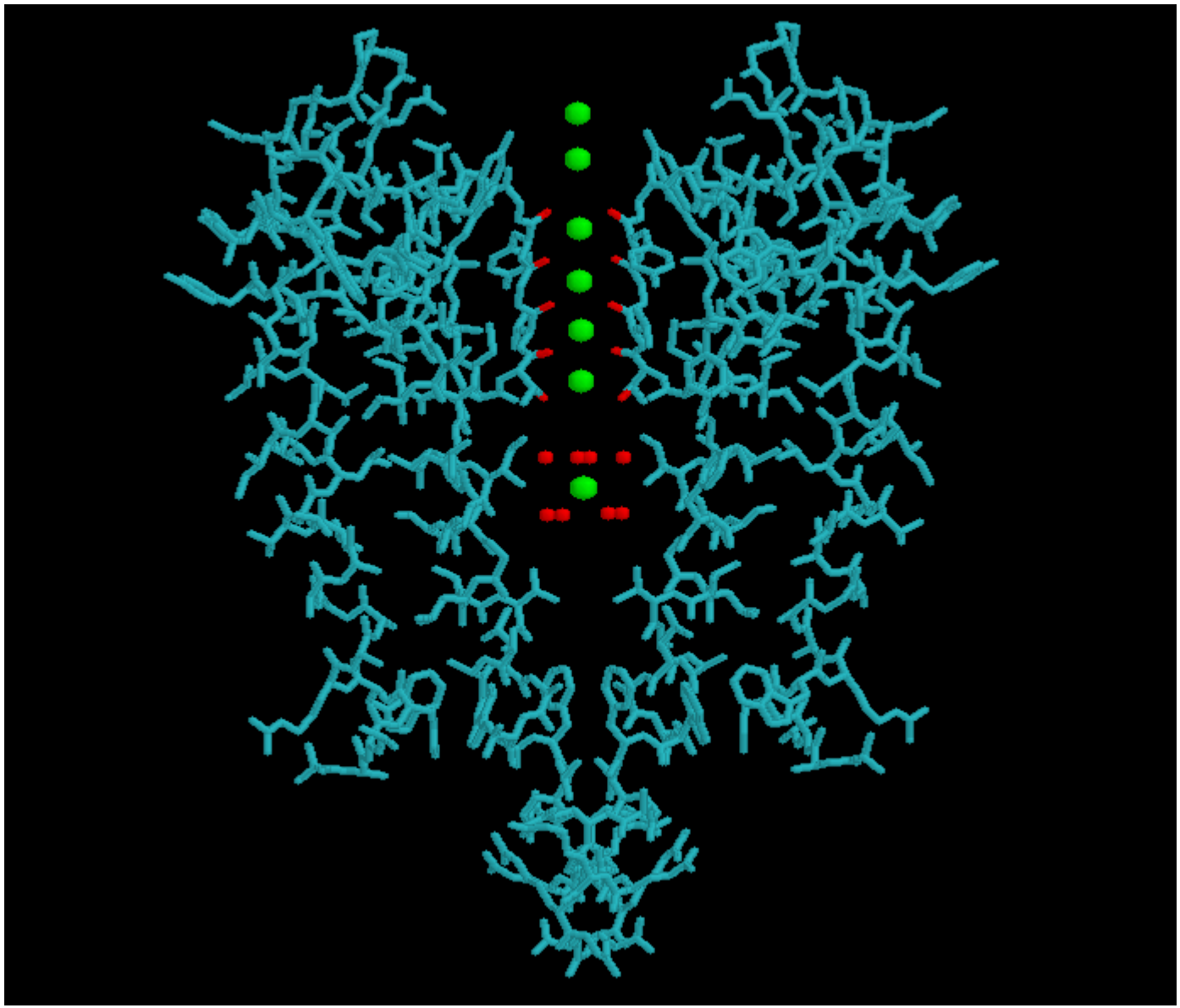
Prochlorococcus

Biologists base their theories about what something does upon what *other* biologists think some other things that look similar do.

Homology of hexokinase across species:

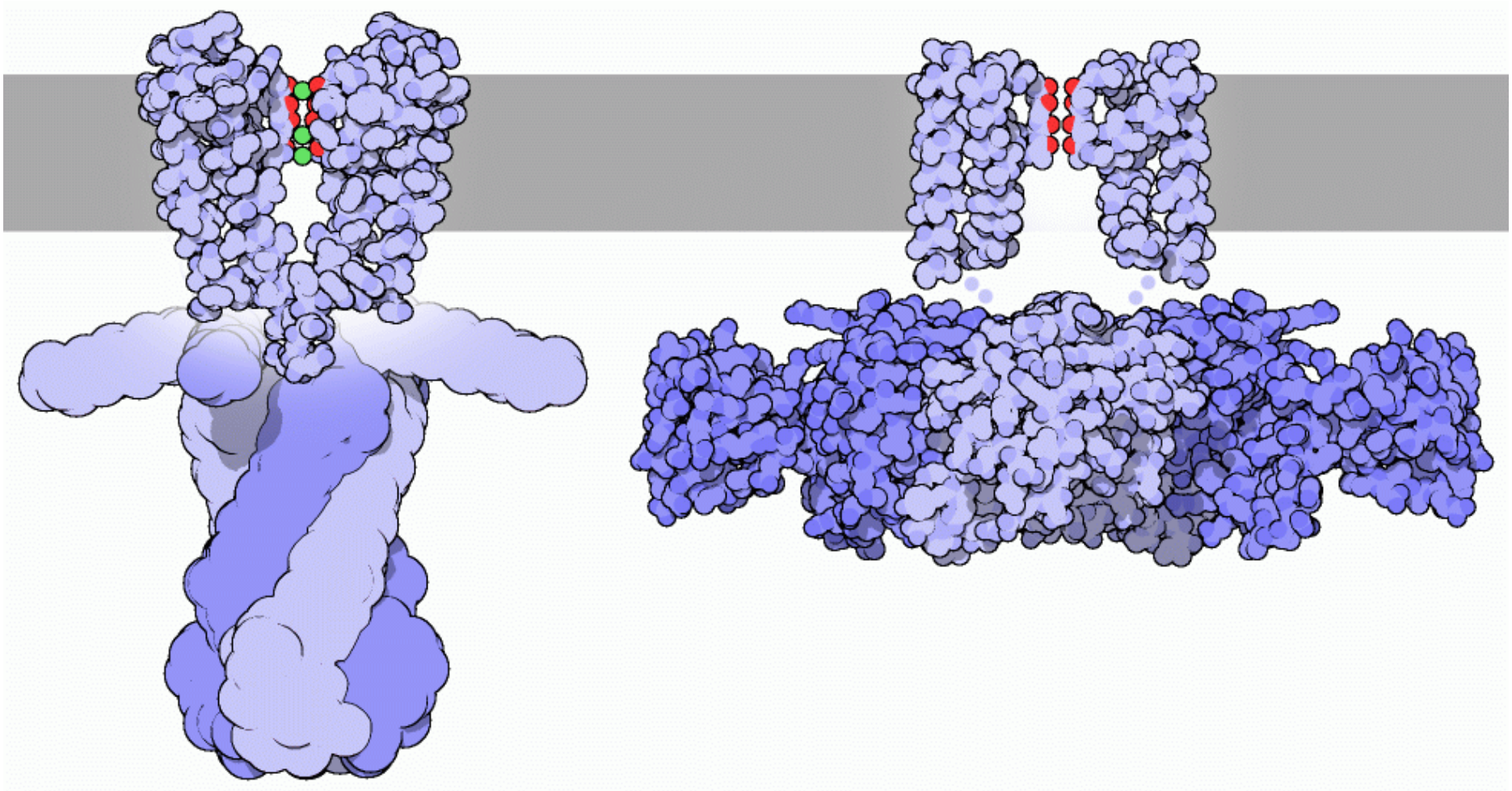
www.bio.davidson.edu/Biology

High-Resolution Solution of a Potassium Channel



www.pdb.org

High-Resolution Solution of a Potassium Channel



www.pdb.org

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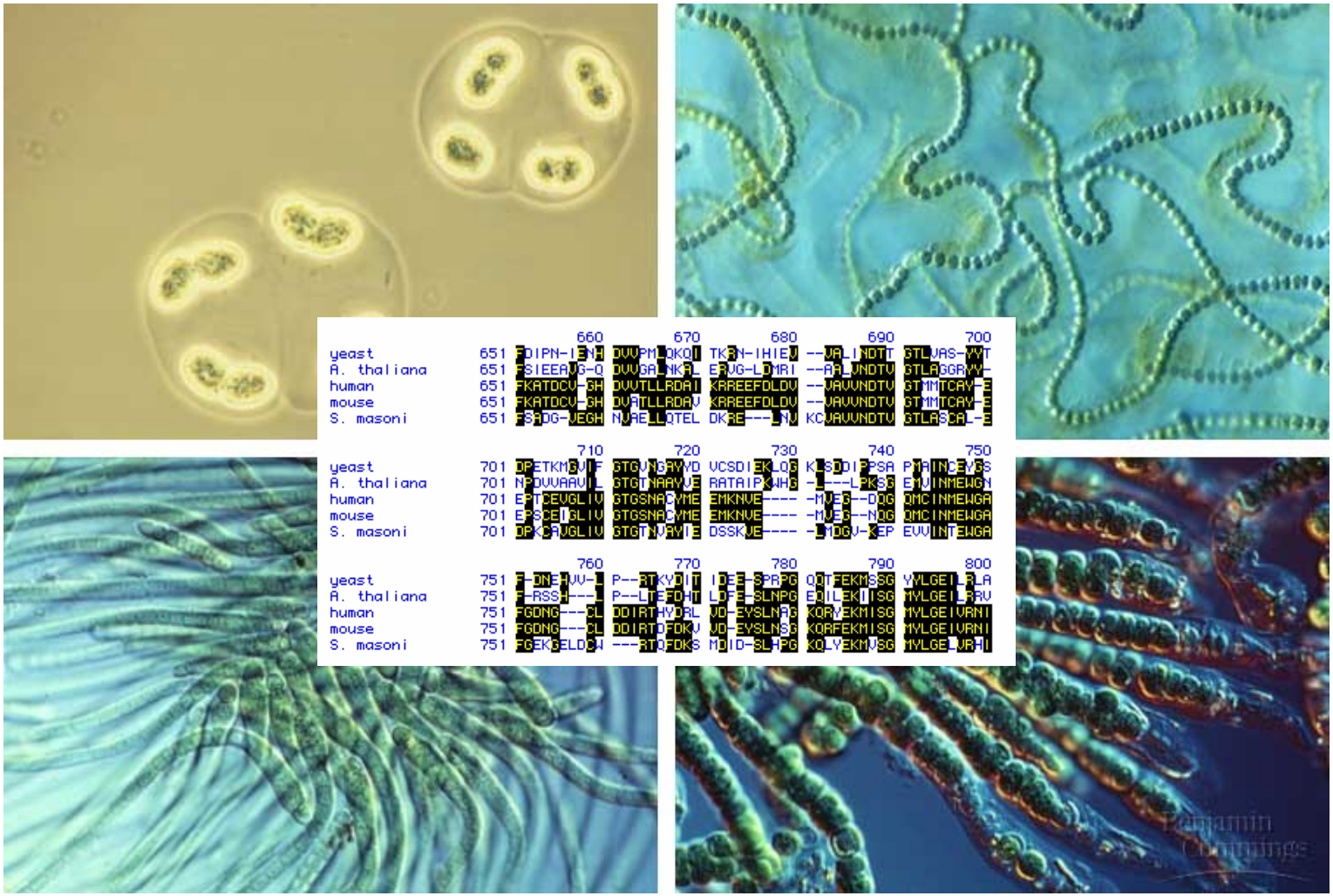
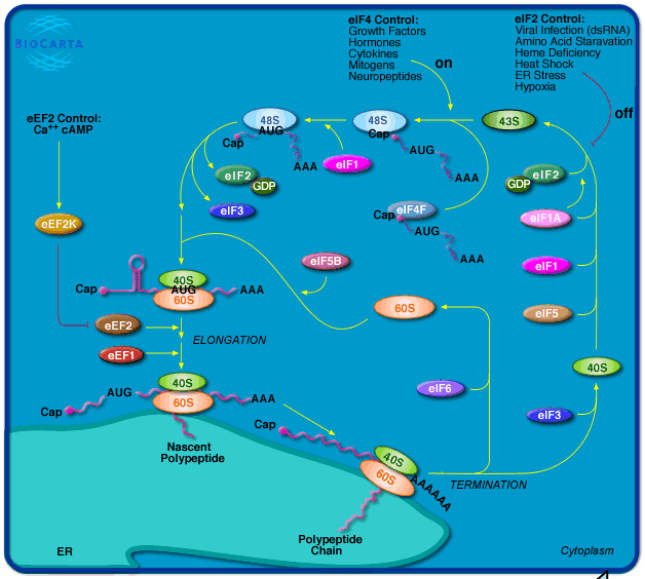
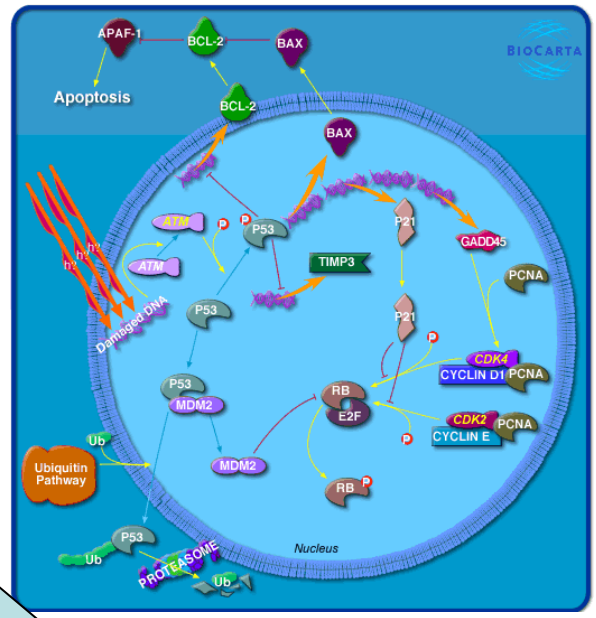
Cyanobacteria

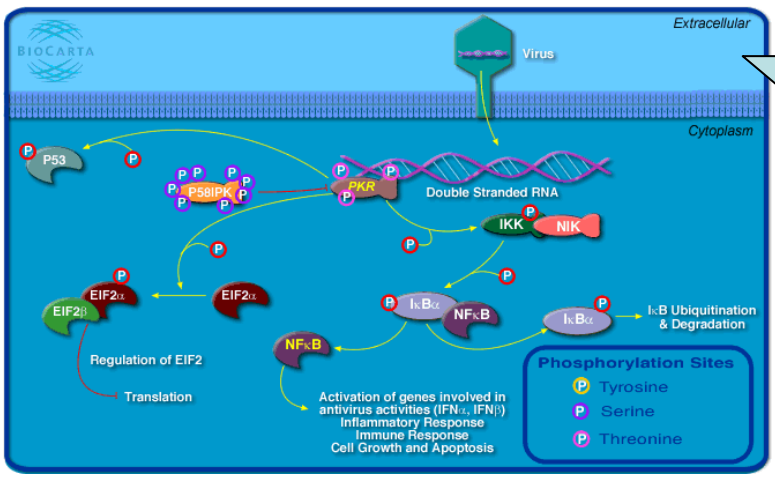


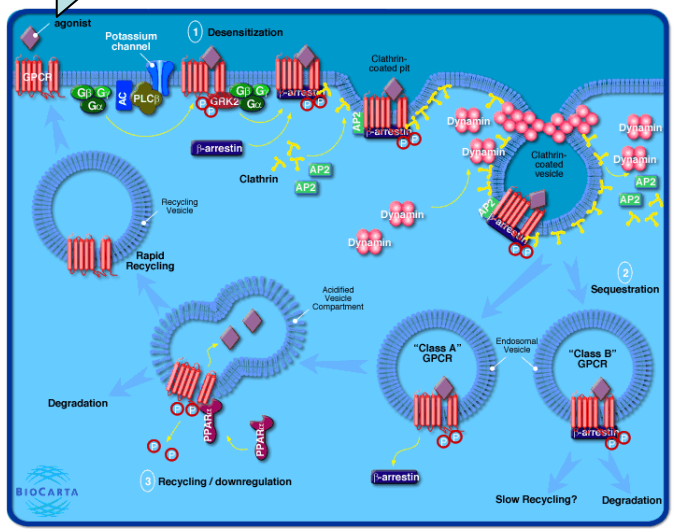
http://www.anselm.edu/homepage/jpitocch/genbios/27-11x1-Cyanobacteria.jpg


BIOCARTA
eIF4 Control:
Growth Factors
Hormones
Cytokines
Mitogens
Neuropeptides
on
eIF2 Control:
Viral Infection (dsRNA)
Amino Acid Starvation
Heme Deficiency
Heat Shock
ER Stress
Hypoxia
off
eEF2 Control:
Ca++ cAMP
eEF2K
48S
AUG
Cap
AAA
eIF1
eIF2
GDP
eIF3
43S
eIF4F
eIF1A
eIF5B
40S
60S
eEF2
ELONGATION
eEF1
eIF6
eIF5
Nascent
Polypeptide
TERMINATION
Polypeptide
Chain
ER
Cytoplasm


BIOCARTA
APAF-1
BCL-2
BAX
Apoptosis
ATM
P53
P21
GADD45
TIMP3
PCNA
Damaged DNA
CDK4
CYCLIN D1
MDM2
RB
E2F
CDK2
CYCLIN E
Ubiquitin
Pathway
Ub
PROTEASOME
Nucleus

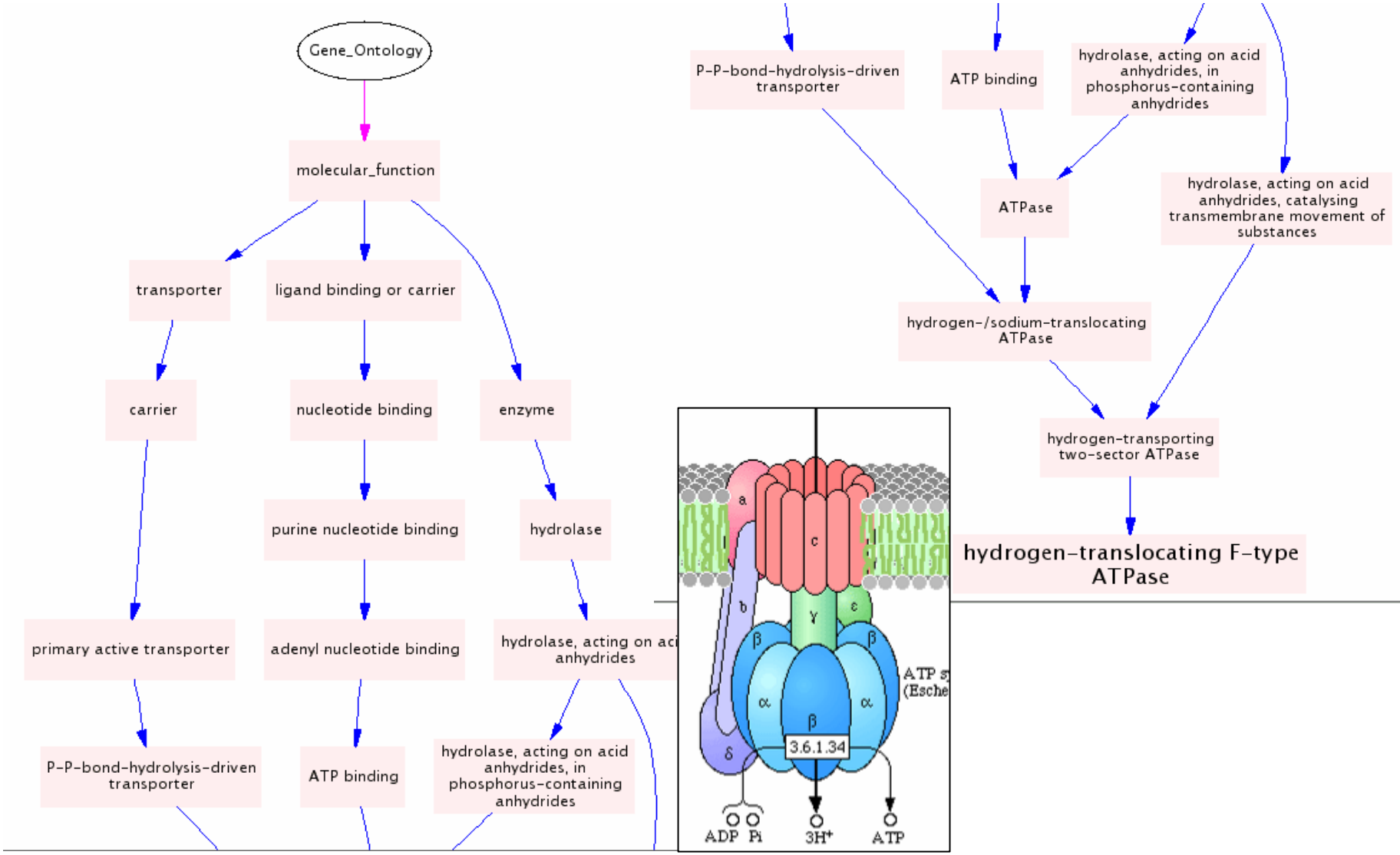
?


BIOCARTA
Extracellular
Virus
Cytoplasm
P53
P58IPK
PKR
Double Stranded RNA
IKK
NIK
EIF2α
EIF2β
IκBα
NFκB
IκB Ubiquitination
& Degradation
Regulation of EIF2
Translation
Activation of genes involved in
antivirus activities (IFNα, IFNβ)
Inflammatory Response
Immune Response
Cell Growth and Apoptosis
Phosphorylation Sites
Tyrosine
Serine
Threonine

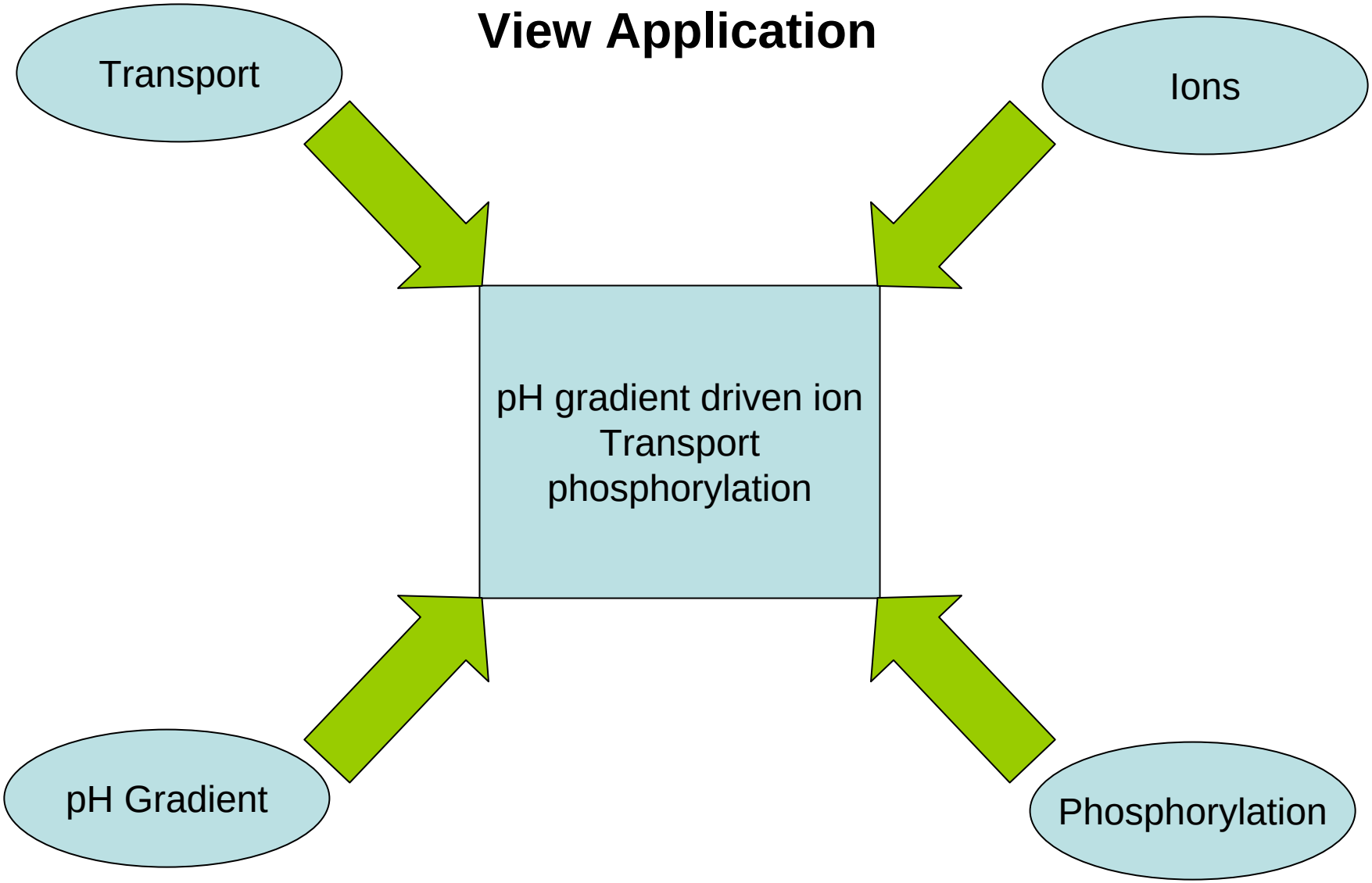

agonist
Potassium
channel
1 Desensitization
GPCR
Gβ Gγ
Gα
PLCβ
GRK2
β-arrestin
Clathrin-
coated pit
AP2
Dynamin
Clathrin-
coated
vesicle
Recycling
Vesicle
Rapid
Recycling
Clathrin
2
Sequestration
Acidified
Vesicle
Compartment
Degradation
PPARγ
"Class A"
GPCR
Endosomal
Vesicle
"Class B"
GPCR
3 Recycling / downregulation
Slow Recycling?
Degradation
BIOCARTA

The Fiction of Function

Gene Ontology



From GenNav, the NIH Gene Ontology Browser


View Application
Transport
Ions
pH gradient driven ion
Transport
phosphorylation
pH Gradient
Phosphorylation

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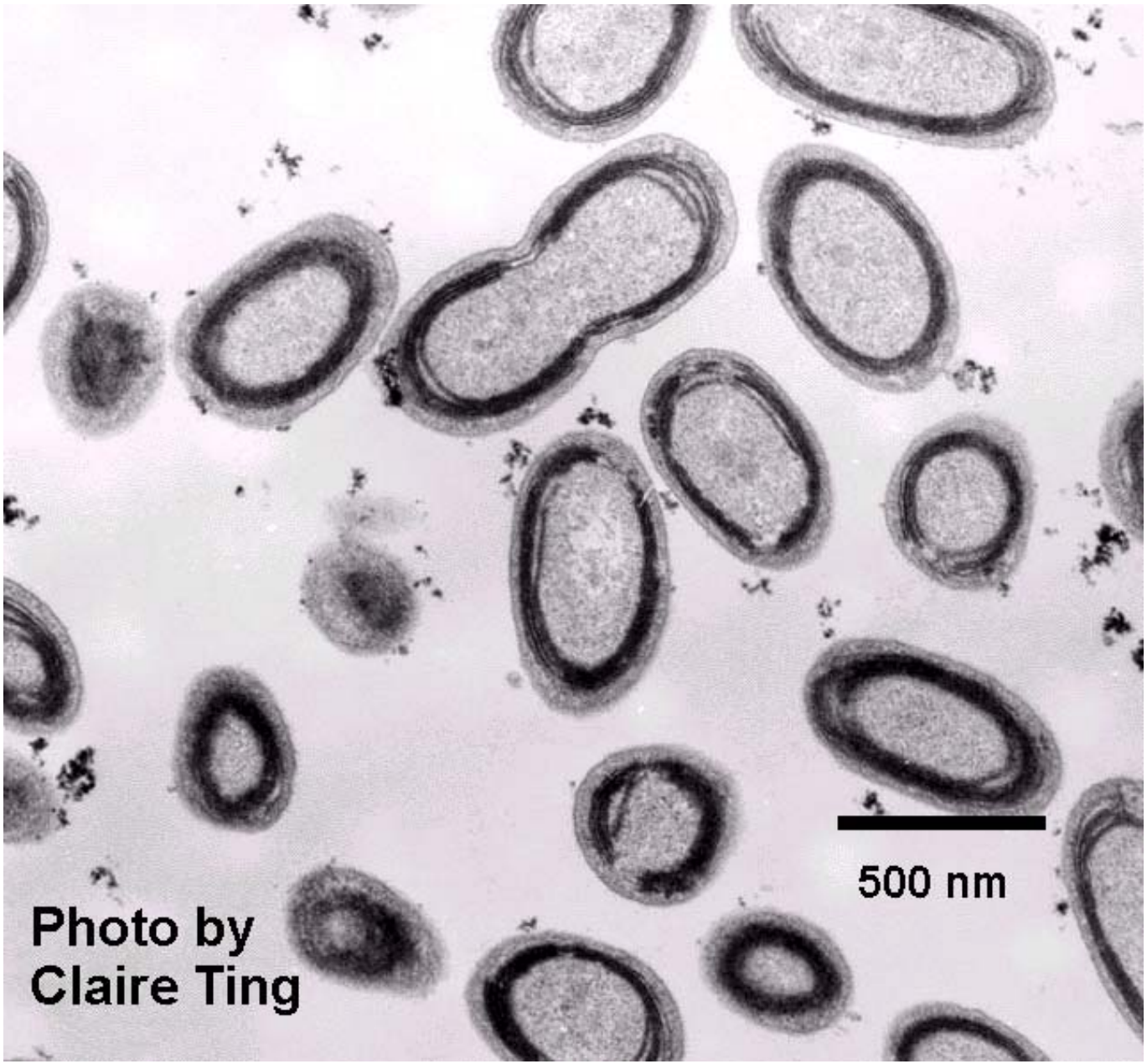
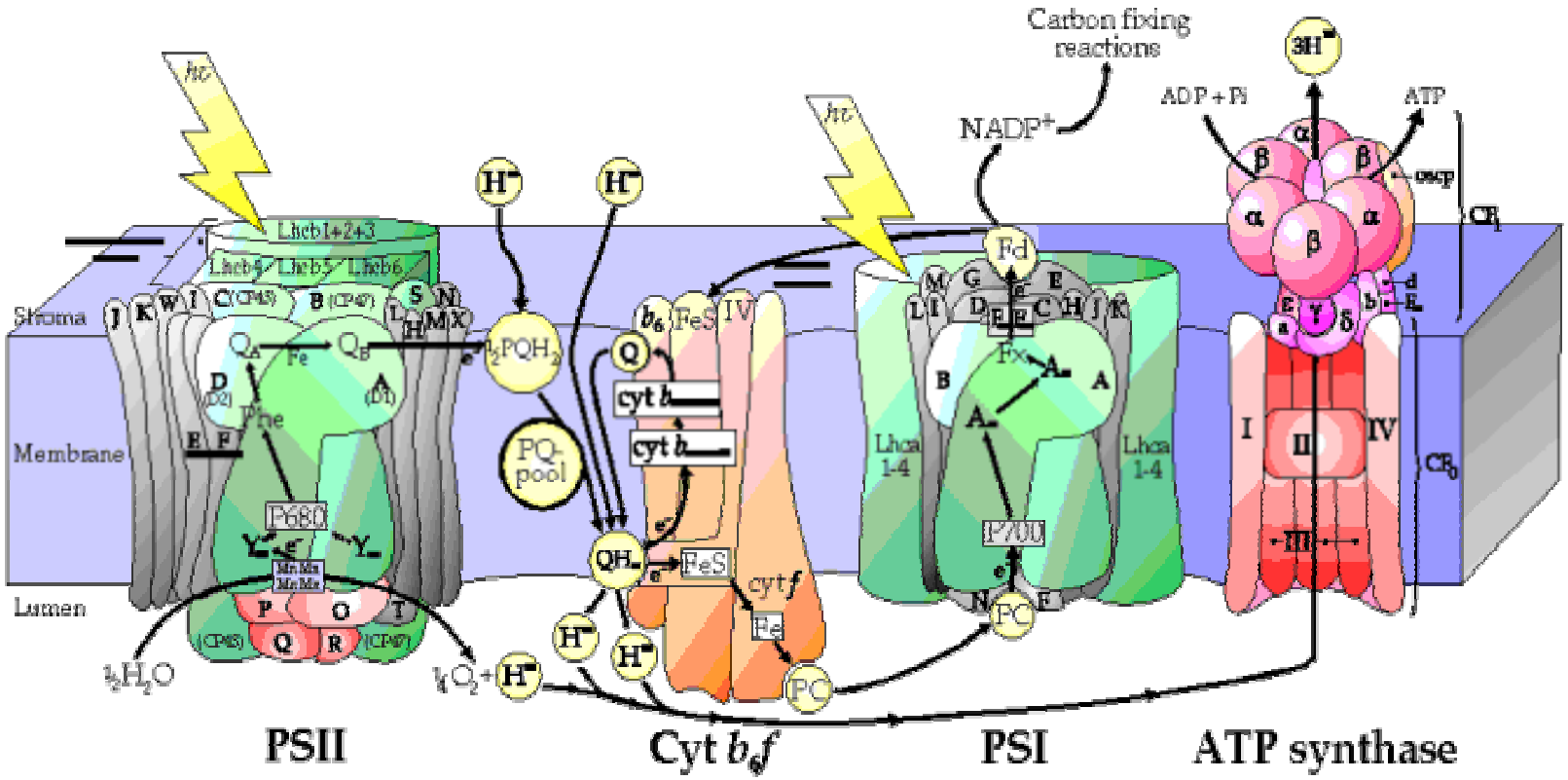
Each of these Demands Symbolic Computing

Prochlorococcus



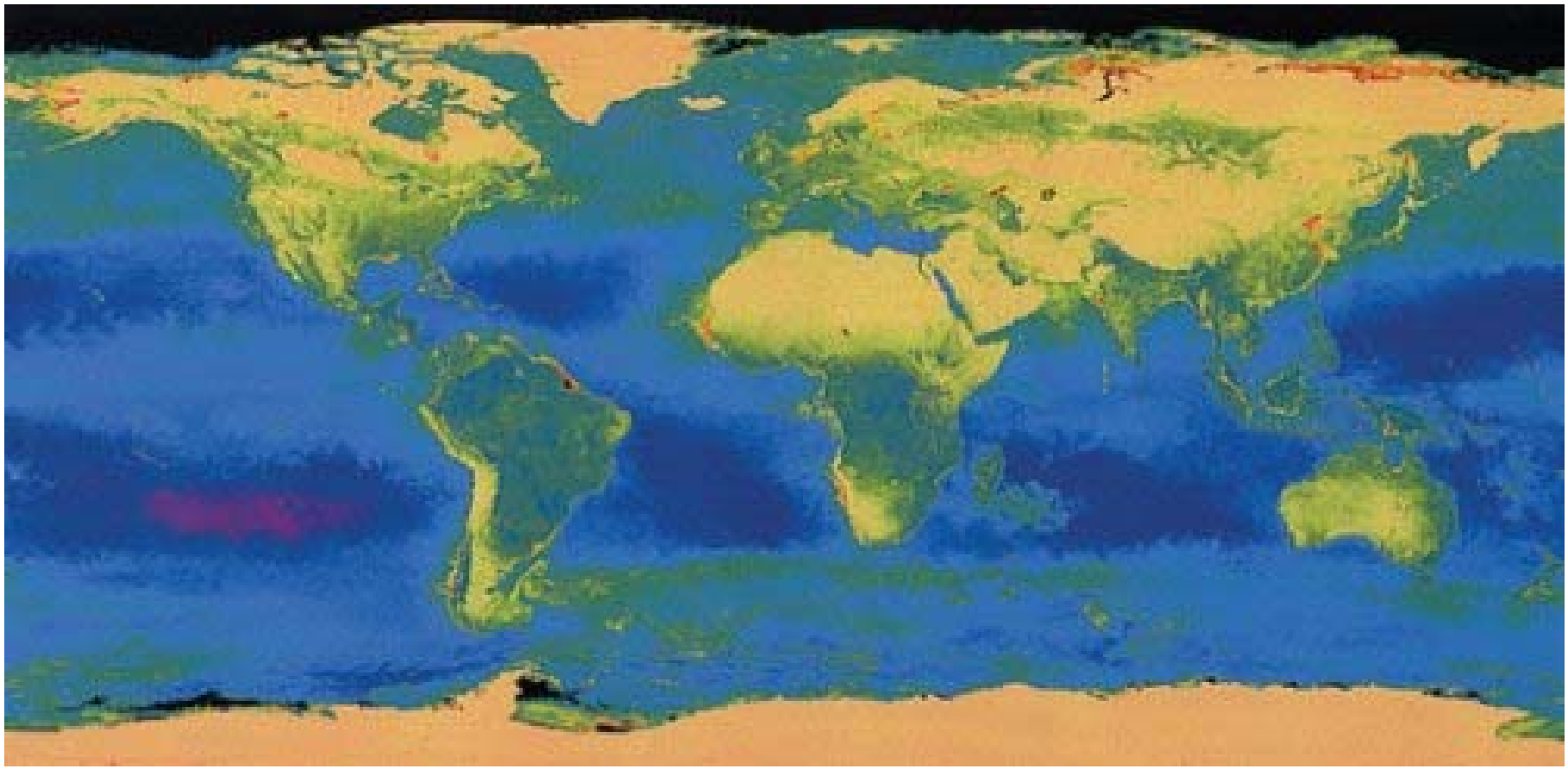
Photosynthesis: The “Turing Test” of biological knowledge representation



PhotoSynthesis (light reactions)

http://www.bio.ic.ac.uk/research/barber/photosystemII.html

Where Prochlorococcus Go; The BioSphere Follows!



Chlorophyll loading (NASA)