ALL ABOUT SYSTEMS BIOLOGY

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Definition of Systems Biology

Wikipedia definition

Systems biology is a biology-based inter-disciplinary study field that focuses on the systematic study of complex interactions in biological systems, thus using a new perspective (holism instead of reduction) to study them.

- discover new emergent properties
- understand better the entirety of processes that happen in a biological system.

Other Definitions

- Systems biology is a comprehensive quantitative analysis of the manner in which all the components of a biological system interact functionally over time (Alan Aderem, Cell, Vol 121, 611-613, 2005. Institute of Systems Biology, Seattle).
- Systems biology is the study of the behavior of complex biological organization and processes in terms of the molecular constituents (Marc W. Kirschner, Cell, Vol 121, 503-504, 2005. Department of Systems Biology, Harvard Medical School).
- Systems biology can be described as "Integrative Biology" with the ultimate goal of being able to predict *de novo* biological outcomes given the list of components involved (Edison T. Liu, Cell, Vol 121, 505-506, 2005. Genome Institute of Singapore).
- "Systems biology" aims at a quantitative understanding of biological systems to an extent that one is able to predict systemic features (Peer Bork and Luis Serrano, Cell, Vol 121, 507-509, 2005. EMBL Germany).

Why is it difficult to define Systems Biology ?

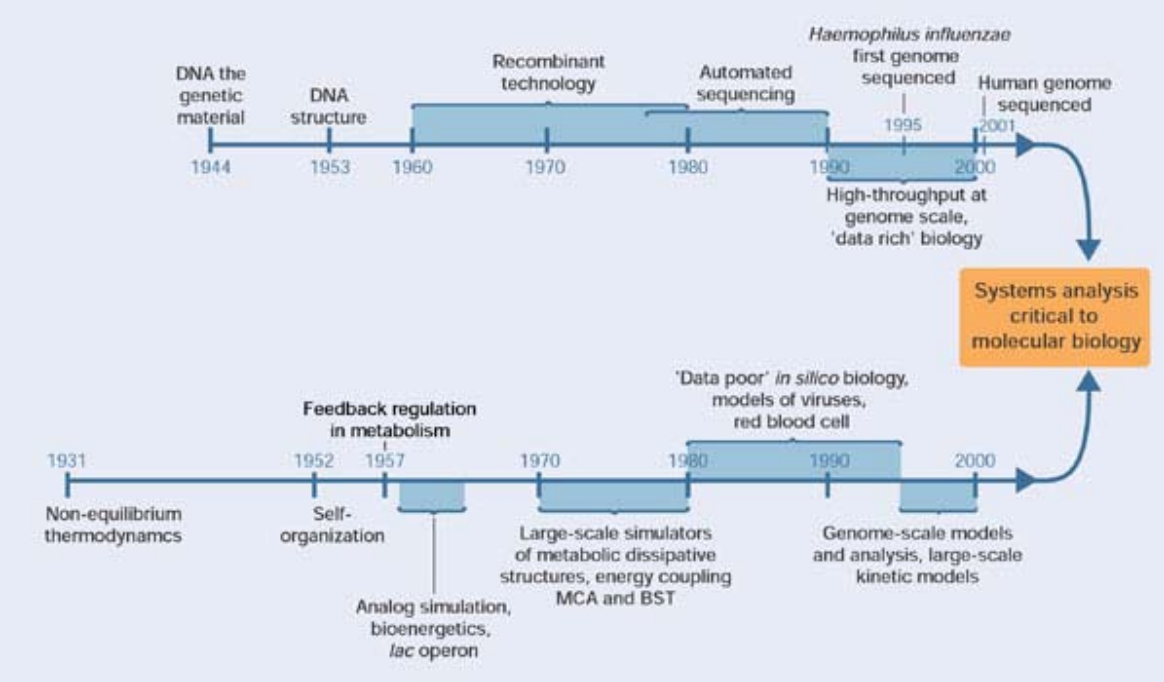
Because there always appears to be a delicate balance between opposing aspects

- Scale: genome-wide vs small scale networks
- Discipline: biological vs physical
- Method: computational vs experimental
- Analysis: deterministic vs probablistic

History of Systems Biology

Two Roots

- Molecular biology, with its emphasis on individual macromolecules.
- formal analysis of new functional states that arise when multiple molecules interact simultaneously.



Hans V Westerhoff & Bernhard O Palsson, *Nature Biotechnology* Vol 22 No 10 Oct 2004

Multi-disciplinary Field

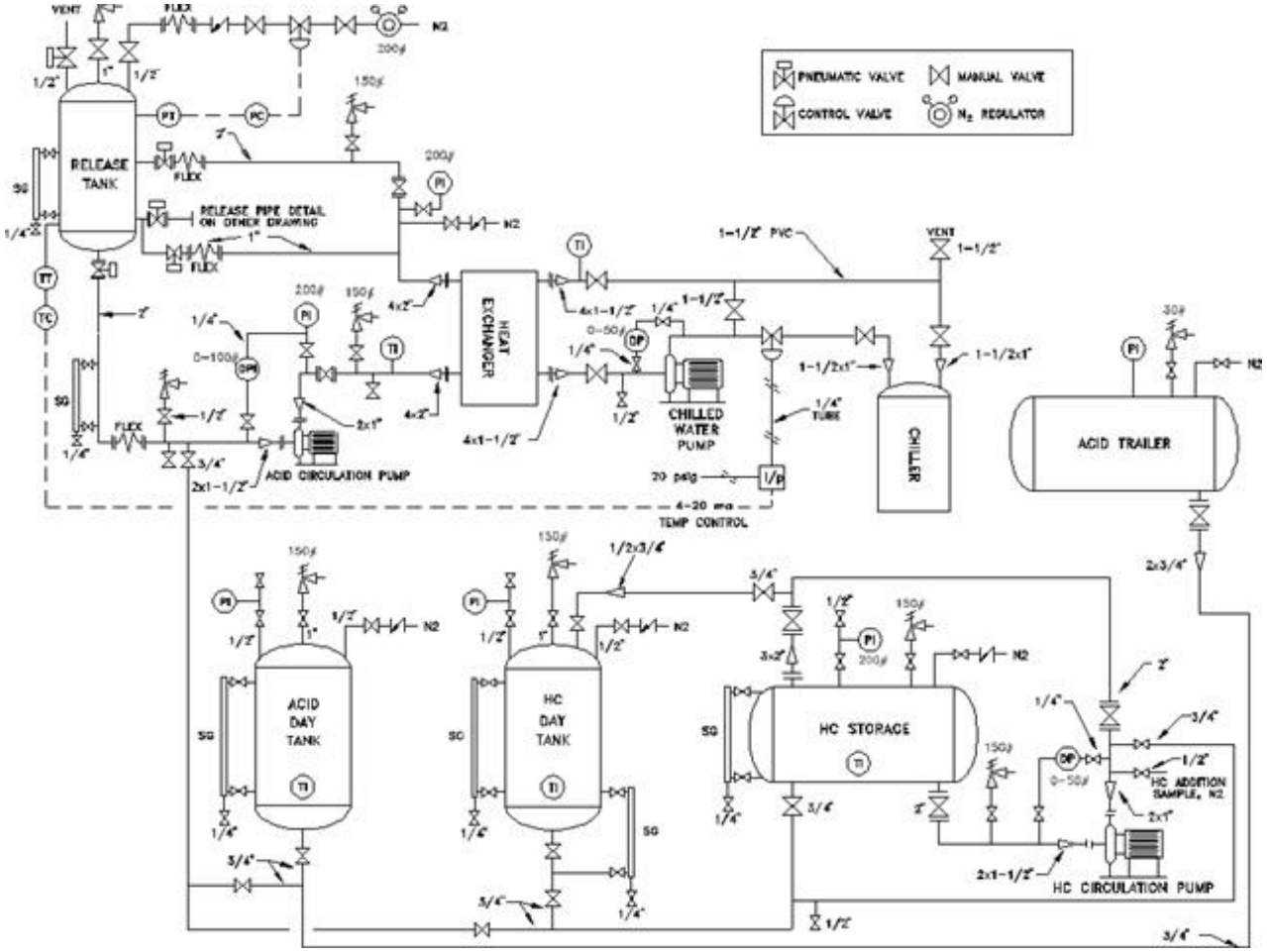
- Engineering Principles
- Nonlinear systems analysis
- Network theory
- Abstract mathematics – representation theory, group theory and graph theory
- Nonlinear Thermodynamics
- Physics
- Chemistry
- Biology

Where do we start ?

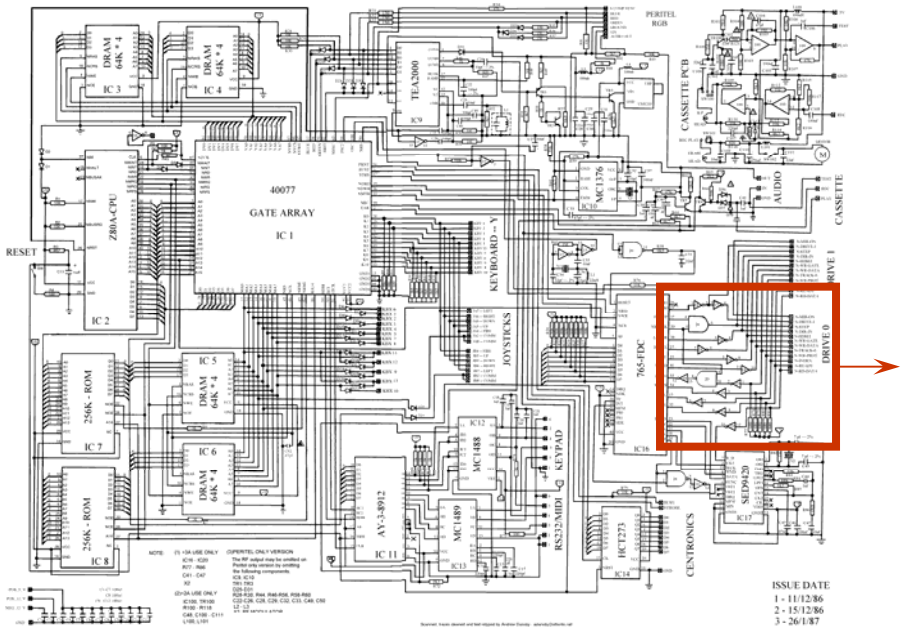
- A living cell can be viewed as a dynamical system in which a large number of different substances react continuously and non-linearly with one another
- It is insufficient to study each part in isolation
- Time domain data of concentrations of biologically important chemicals in living are now available or possible to measure

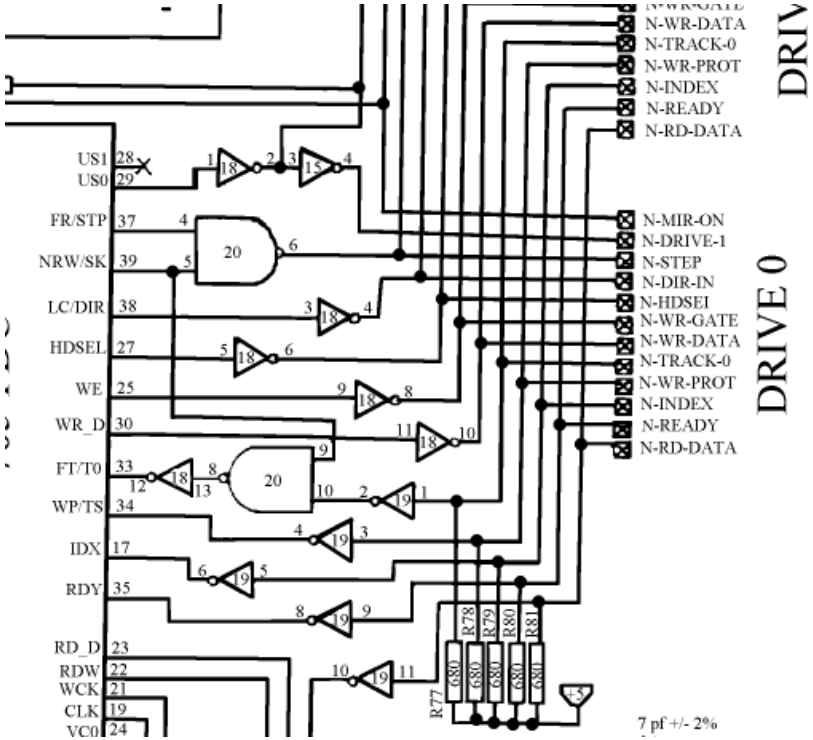
It is possible to start with observed time-domain concentrations of substances and automatically create both the topology of the network of chemical reactions and the rates of each reaction?

Compare with a Chemical Plant



AND Compare with an Electronic Circuit Diagram



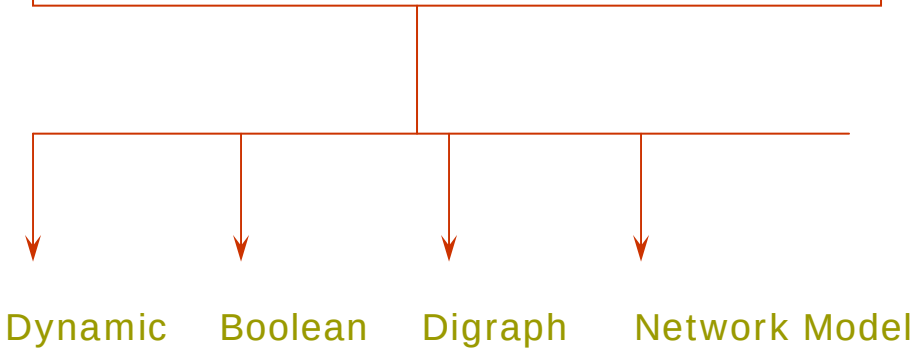


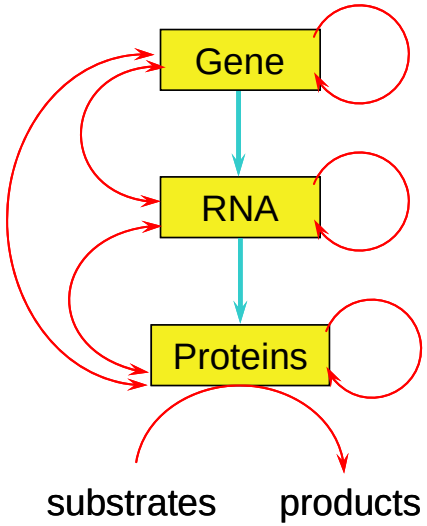
Analogies are not perfect

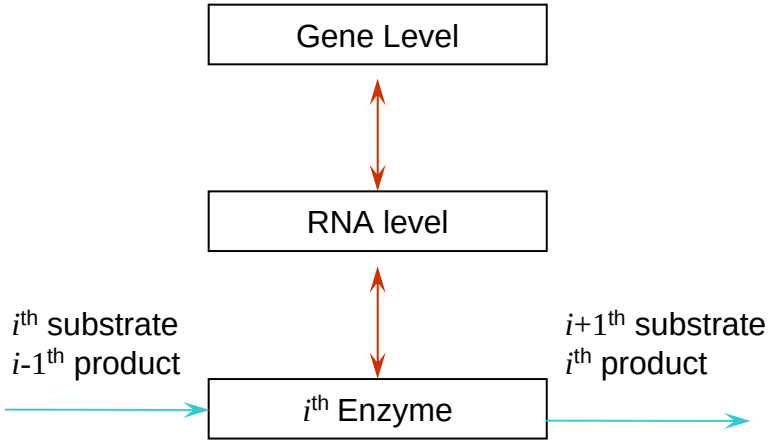
- There are no pipes lines inside the cell
- Reactants and products are not restricted with 'reactors'
- Characteristic times of cellular events vary over a wide range (10^{-9} s to 10^{3} s)
- Petroleum plants cannot self replicate
- Signal molecules are not restricted to electrical channels
- Genetics circuits are not restricted by "circuit boards"
- Cells generate their own energy
- Cells are "ALIVE"

The levels of cellular information

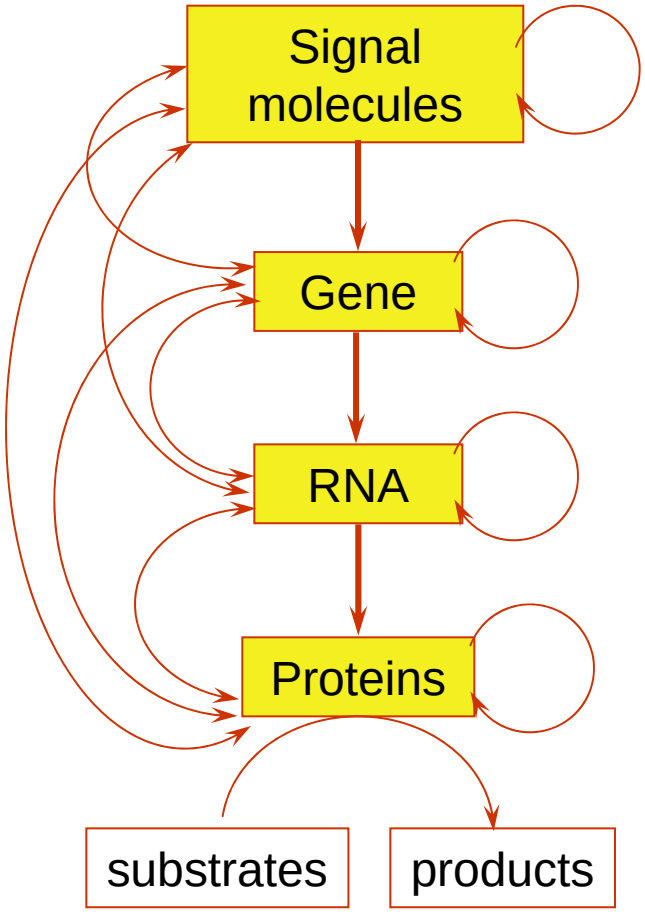
- Define the interactions for each gene, RNA and protein
- Define each of the reactions for this metabolic network
- Examine its behavior







Create a wiring diagram



- There are multiple levels of interaction
- At each level, nearly all processes are nonlinear
- Kinetic parameters are extremely difficult find because the questions being asked are very different

Models are computationally intensive. However, there is a need for theoretical analysis because it will not be feasible to carry out all the experiments required to address a problem

Method of approach

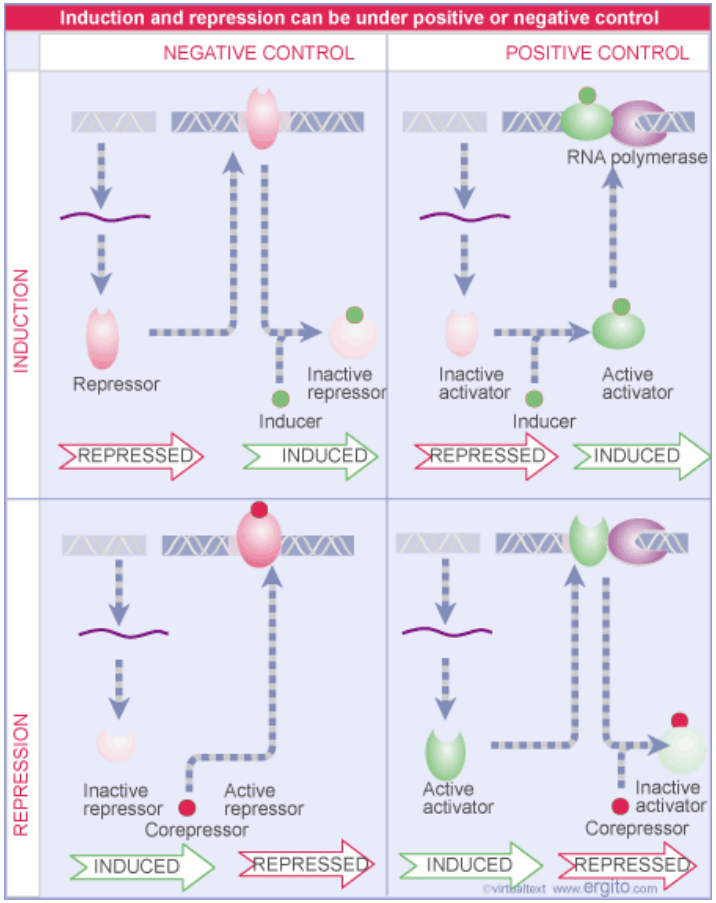
- Study the properties of individual signaling elements, then elementary circuits
- Then try to understand the more complex networks, perhaps in the same way that electrical engineers work their way up from the properties of resistors, capacitors and diodes, to those of simple circuits and, finally, complex devices.
- Then follow the chemical engineers in building up a cell factory using electrical (=signals, gene regulation), mechanical (=biophysics, membrane) and chemical (=cellular processes)

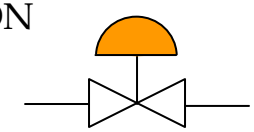
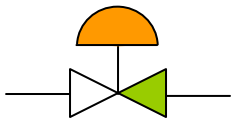
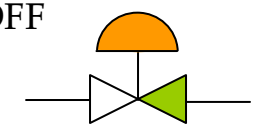
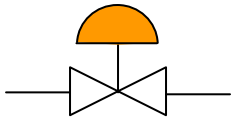
Mechanism

Negative and Positive Control

Defined by the response of the operon when no regulator protein is present

- Genes under negative control are expressed unless they are switched off by a repressor protein
  - Fail-safe mechanism: cell is not deprived of these enzymes even if the regulator protein is absent
- Genes under positive control, are expressed only when an active protein regulator is present
  - Not clear how this mechanism evolved; clearly, either extrinsic or intrinsic events are necessary for positive control to trigger

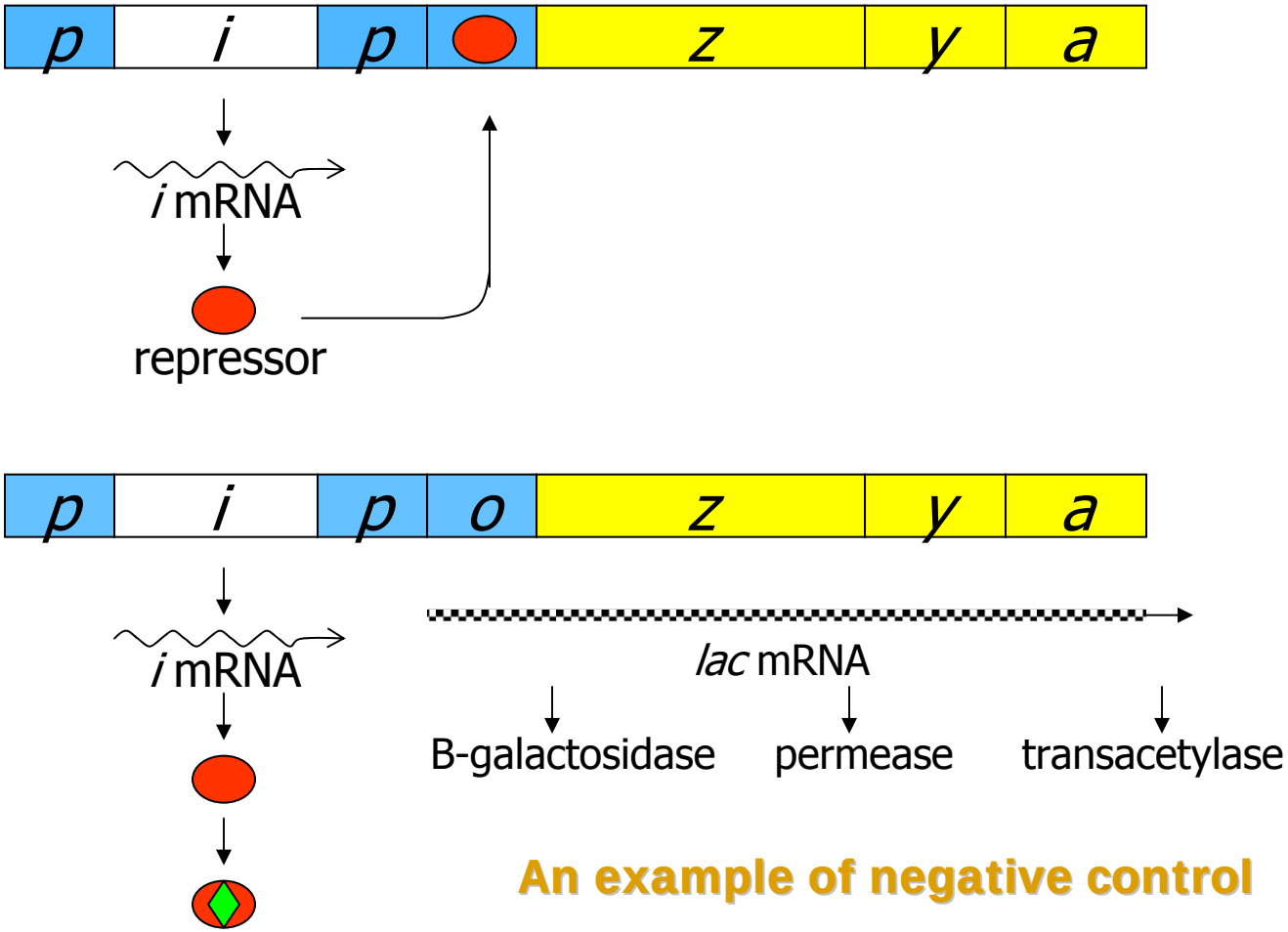


Normally ON 	Normally OFF 
Normally OFF 	Normally ON 

Nature of regulation

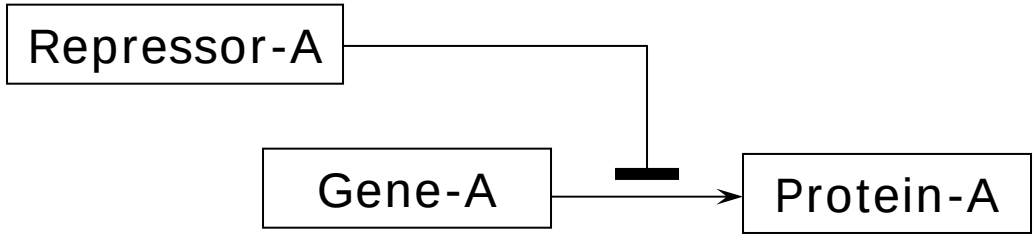
1, 0, [0, 1]

Negative Control of Lactose Operon

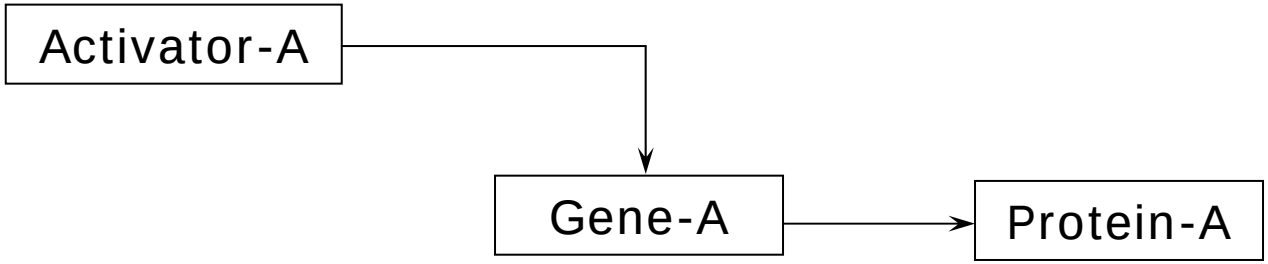


An example of negative control

Depiction of negative and positive control

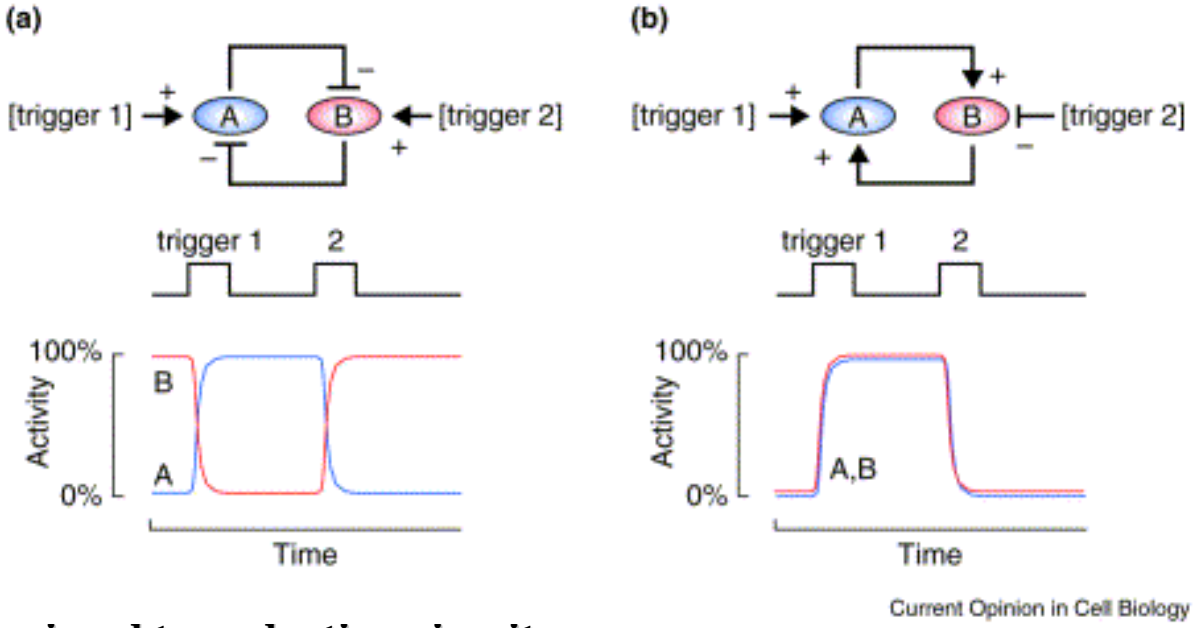


Negative control



Positive control

Double negative feedback loop



Bistable signal transduction circuits

- A double-negative feedback loop. In this circuit, protein A (blue) inhibits or represses B (red), and protein B inhibits or represses A. Thus there could be a stable steady state with A on and B off, or one with B on and A off, but there cannot be a stable steady with both A and B on or both A and B off. Such a circuit could toggle between an A-on state and a B-on state in response to trigger stimuli that impinge upon the feedback circuit.
- A positive feedback loop. In this circuit, A activates B and B activates A. As a result, there could be a stable steady state with both A and B off, or one with both A and B on, but not one with A on and B off or *vice versa*. Both types of circuits could exhibit persistent, self-perpetuating responses long after the triggering stimulus is removed.

Feedback Regulation Motif in Genetic Circuits

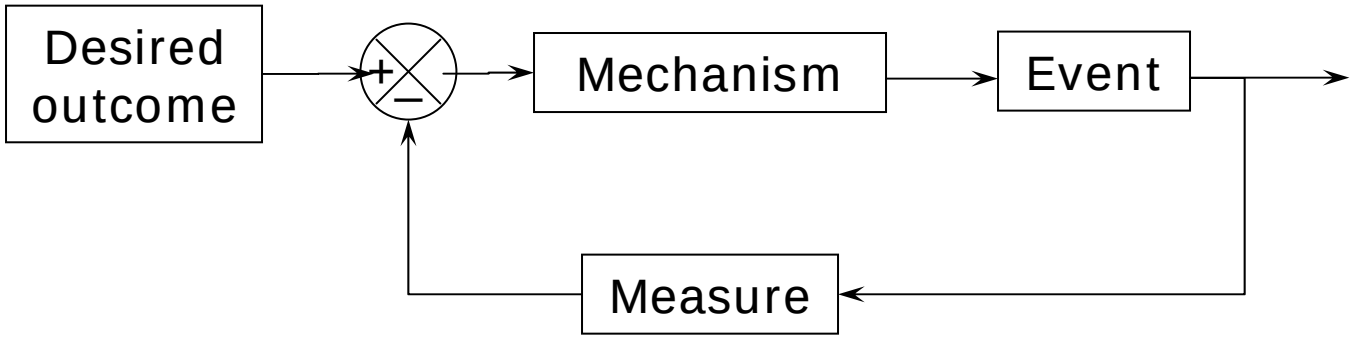
Regulation

Encarta Dictionary: an official rule, law, or order stating what may or may not be done or how something must be done

Control Theory: control of a variable at desired set point or trajectory by manipulating input variables

Biology: the phenomenon by which certain biomolecules either directly or indirectly alter the rate of synthesis of other biomolecules

Related terms: regulator genes, regulator proteins, regulator RNA, regulatory networks

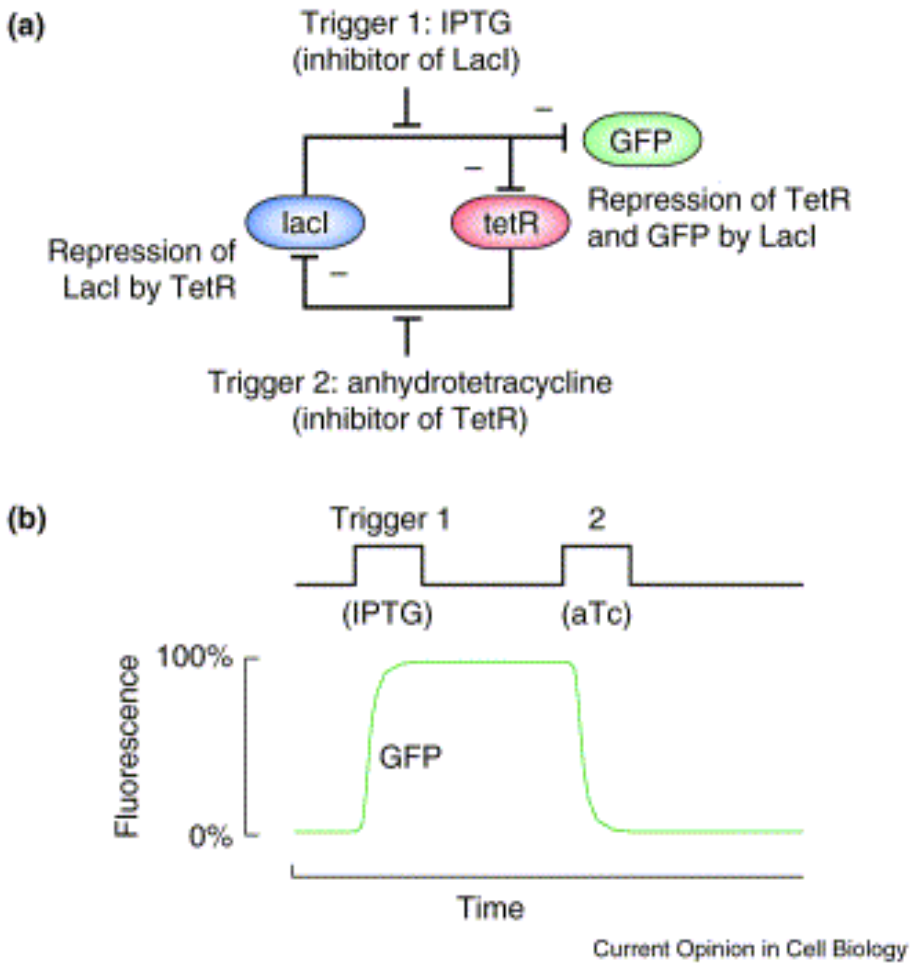


Negative feedback can bring about oscillations

Examples of Genetic Circuits

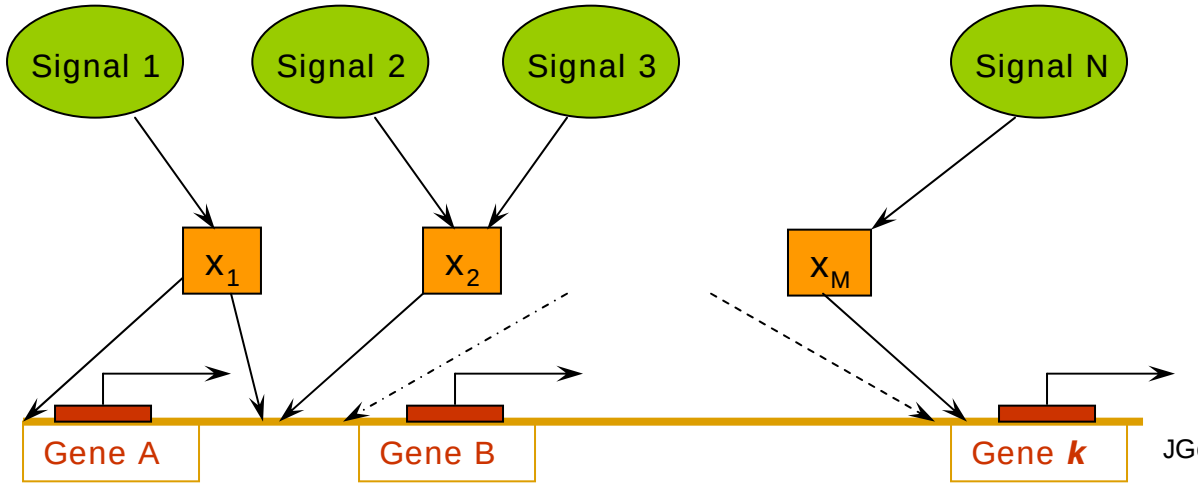
a) Design of the system {Gardner *et al.* genetic toggle switch in *Escherichia coli*. *Nature* 2000,403:339-342} engineered two double-negative feedback systems into *E. coli*. In the system shown here, LacI represses the expression of TetR (and GFP, used as a reporter of the status of *tetR* transcription), and TetR represses the expression of LacI.

b) Response of the system. The system could be made to toggle between the TetR-off and TetR-on states by the addition of external trigger stimuli: IPTG to disinhibit *tetR*, and anhydrotetracycline (aTc to disinhibit *lacI*.



Transcription Networks

- The cells requires different proteins for different circumstances
  - PTS proteins for transport of sugar from environment into cytosol
  - Different repair proteins if cell is damaged
- This information processing is carried out largely by ***transcription networks***

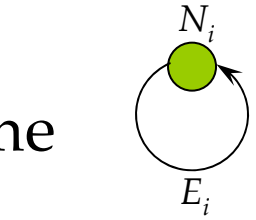


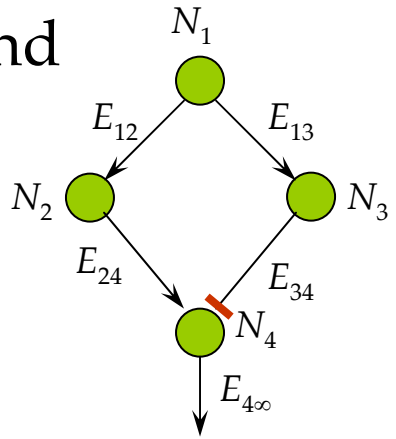
Nodes and Edges

In the context of genetic circuits or gene networks, a node represents an active biological species such as a gene, enzyme or signal molecule. Likewise, an edge depicts the connection and the nature of the connection for between them

Self edge: an edge that starts and ends on the same node

Directed edge: an edge that carries information and indicates the direction of movement of that information





Graphs

A graph G is a finite nonempty set V together with an irreflexive symmetric relation R on V. Since R is symmetric, for each ordered pair $(u, v) \in R$, the pair (v, u) also belongs to R. We denote by E the symmetric pairs in R.

Consider for example the graph G defined by

$V = \{v_1, v_2, v_3, v_4\}$ together with the relation

$R = \{(v_1, v_2),(v_1, v_3), (v_2, v_1), (v_2, v_3),(v_3, v_1)(v_3, v_2), (v_3, v_4),(v_4, v_3)\}$

In this case,

$E = [\{(v_1, v_2), (v_2, v_1), (v_3, v_1) (v_1, v_3), (v_2, v_3), (v_3, v_2), (v_3, v_4), (v_4, v_3)\}]$

V is the vertex set

The number of vertices is called the order of G

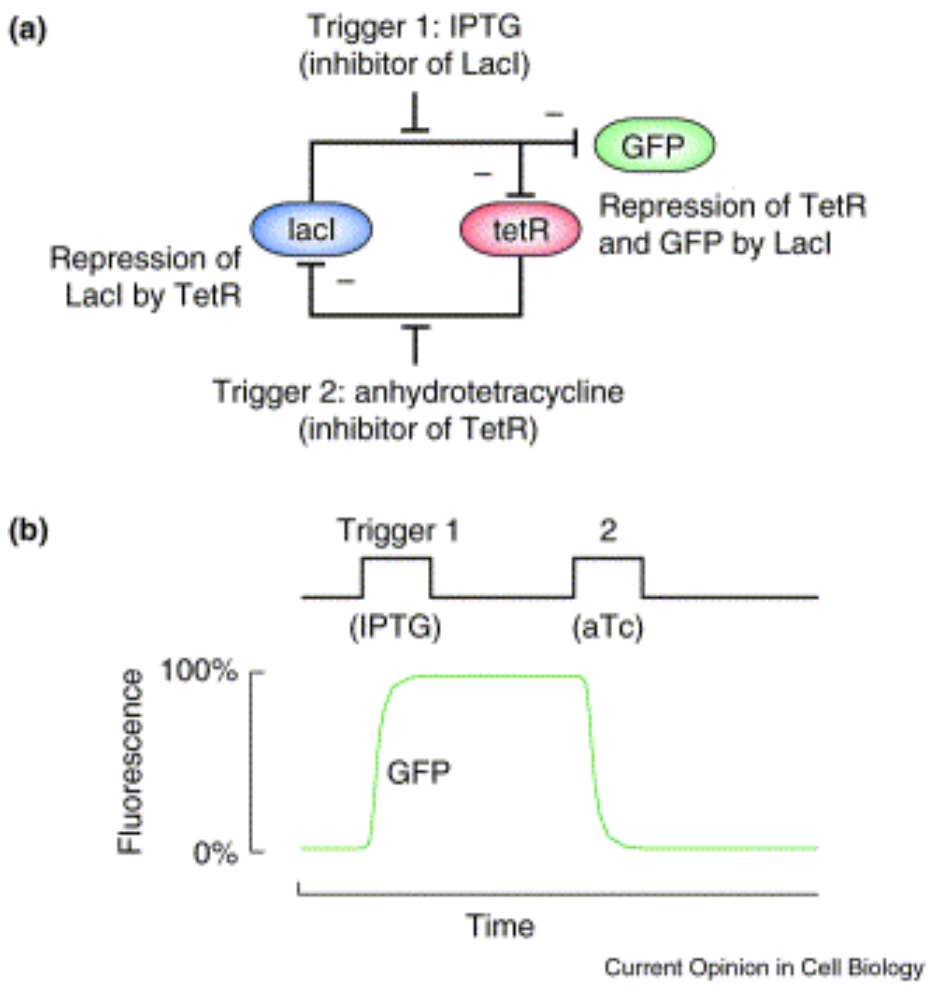
Each element of E consists of two symmetric ordered pairs from R

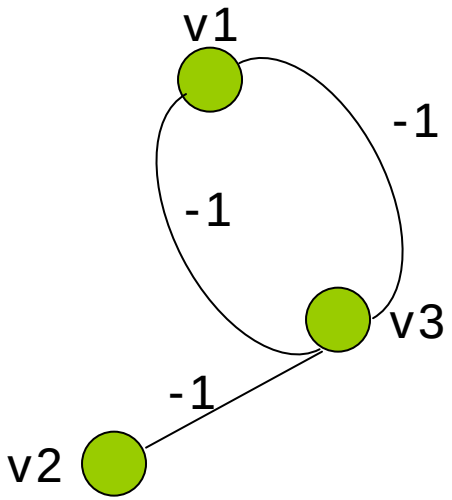
E is called the *edge set* of G

Hence

$|V|$ = order of G and $|E|$ = size of G

An example


(a)
Trigger 1: IPTG
(inhibitor of LacI)
GFP
LacI
TetR
Repression of TetR
and GFP by LacI
Repression of
LacI by TetR
Trigger 2: anhydrotetracycline
(inhibitor of TetR)
(b)
Trigger 1
2
(IPTG)
(aTc)
100%
0%
Fluorescence
GFP
Time
Current Opinion in Cell Biology


v1
-1
-1
v3
-1
v2

Circadian Clocks

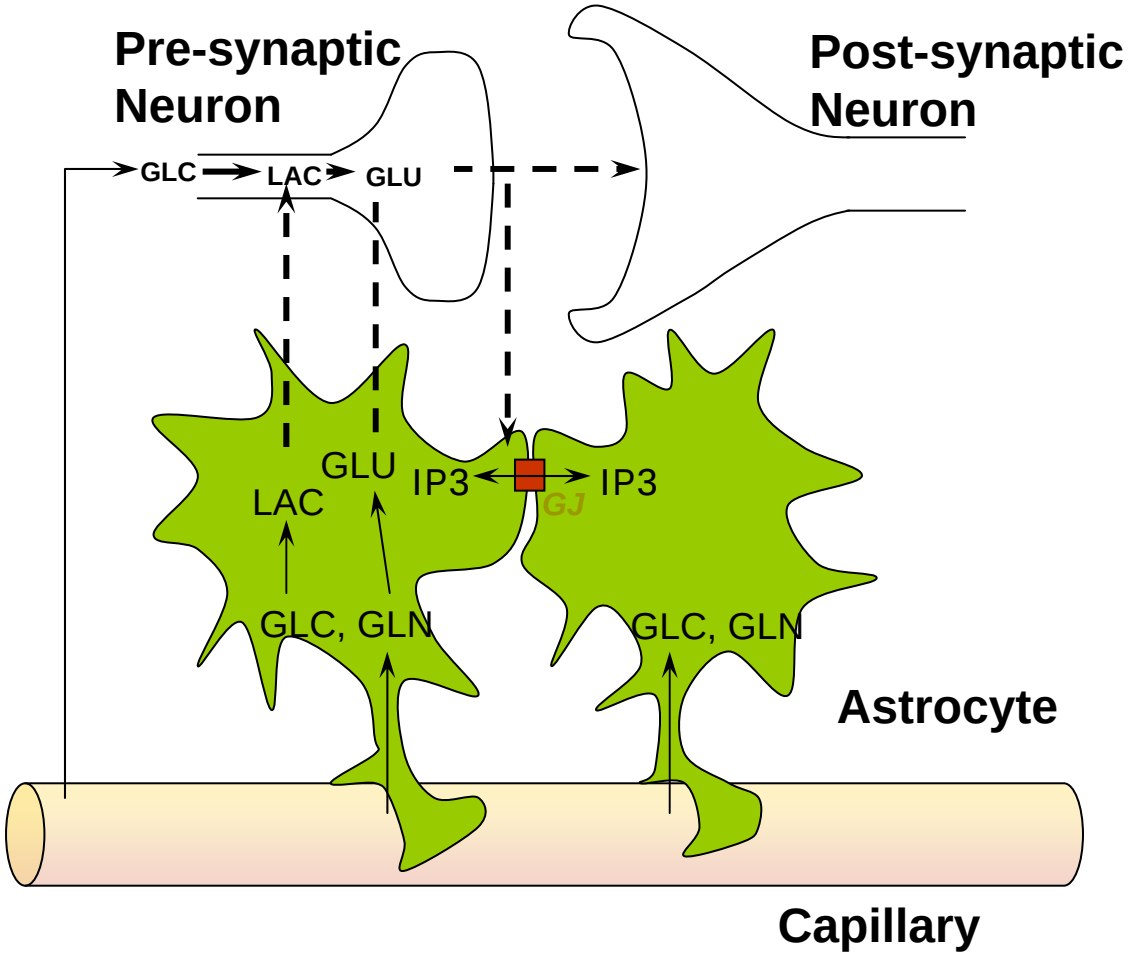
- Cyclic behavior exhibited by genetic circuits
- It is possible to describe these changes by using ordinary differential equations
- Code it in MATLAB (for example)

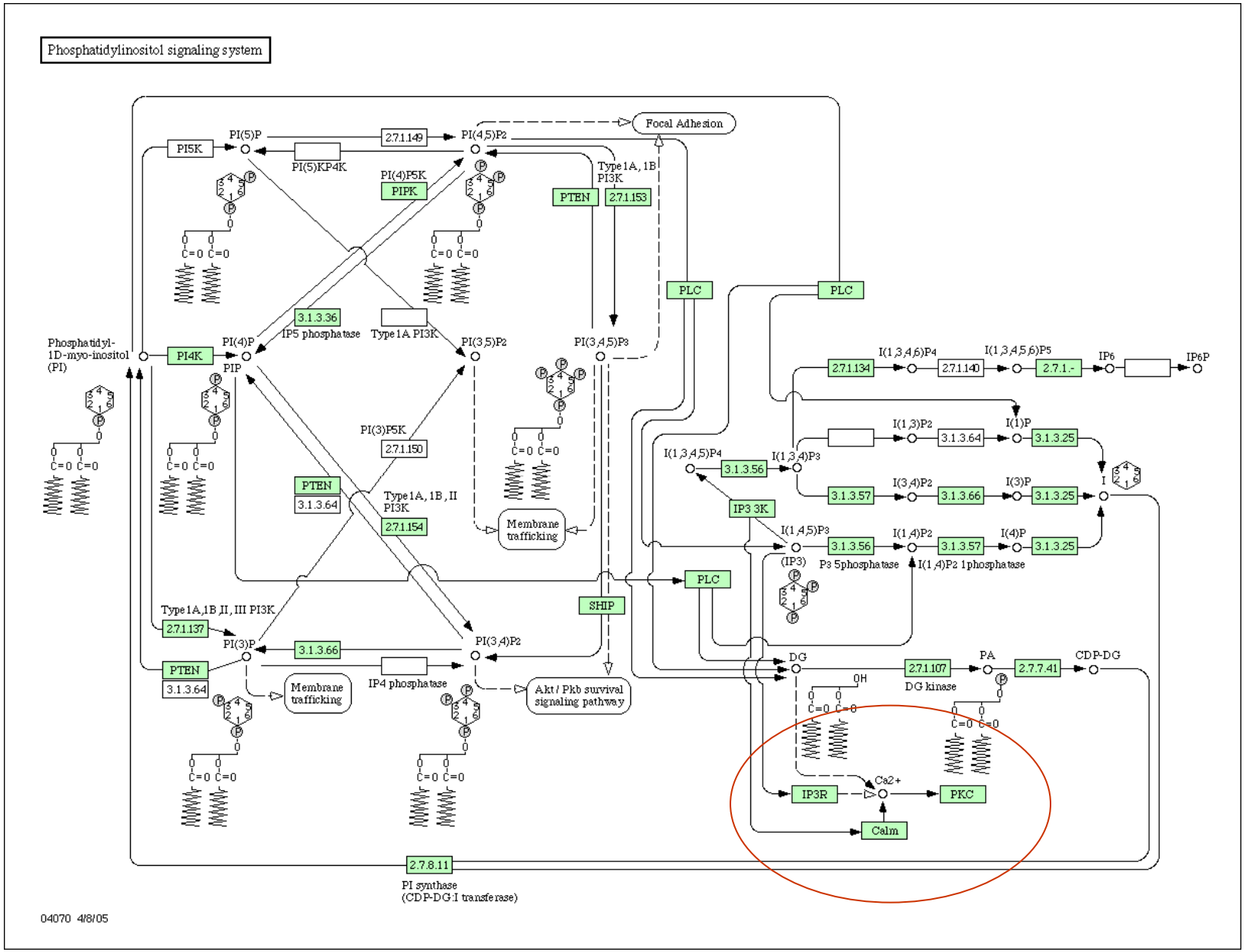
Role of Ca2+ Signaling in Neurodegenerative disorders

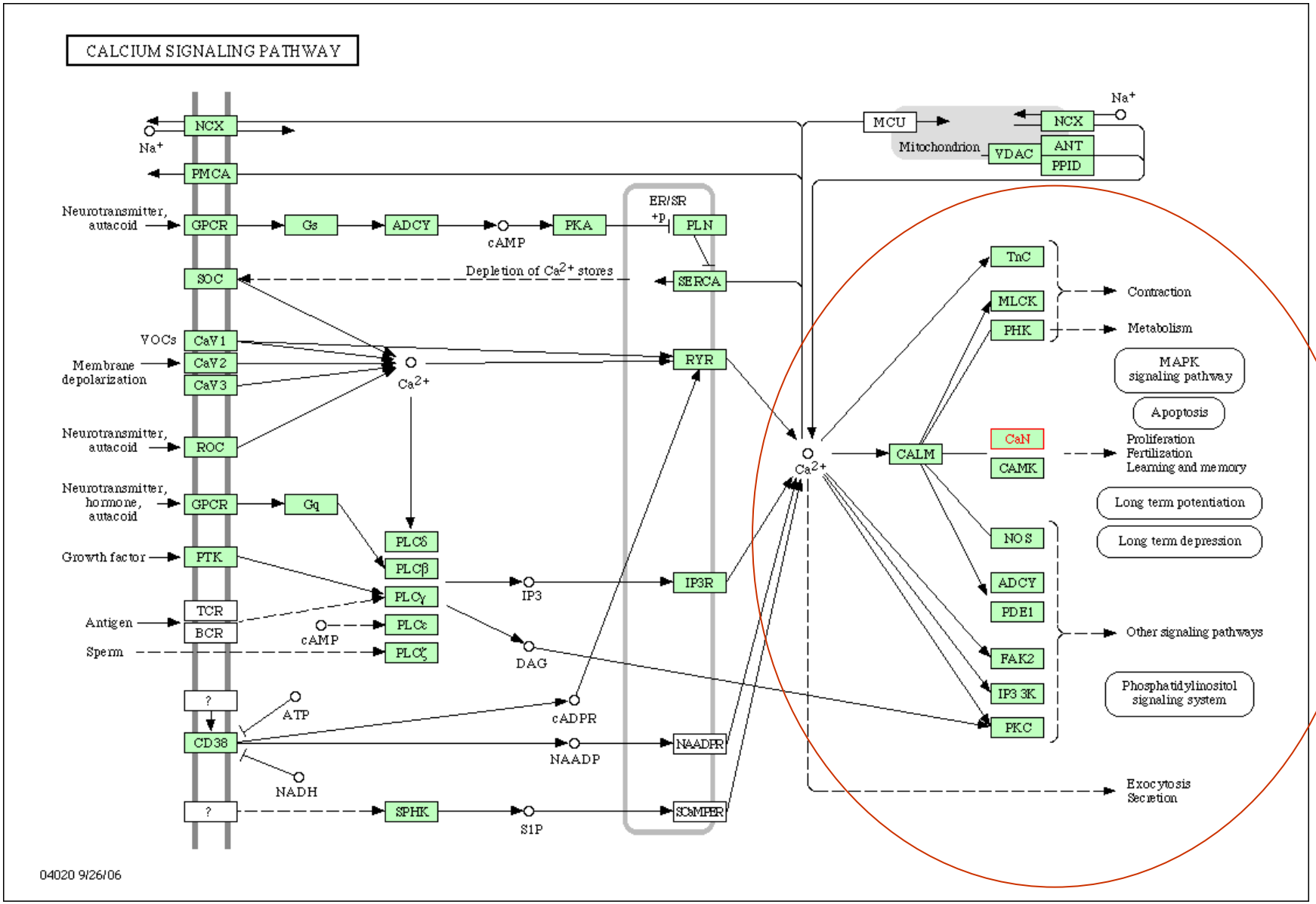
- A sustained high level of Ca2+ can lead to cell apoptosis
- How easy/difficult is it for this to happen?
- What kind of failures can lead to these conditions?

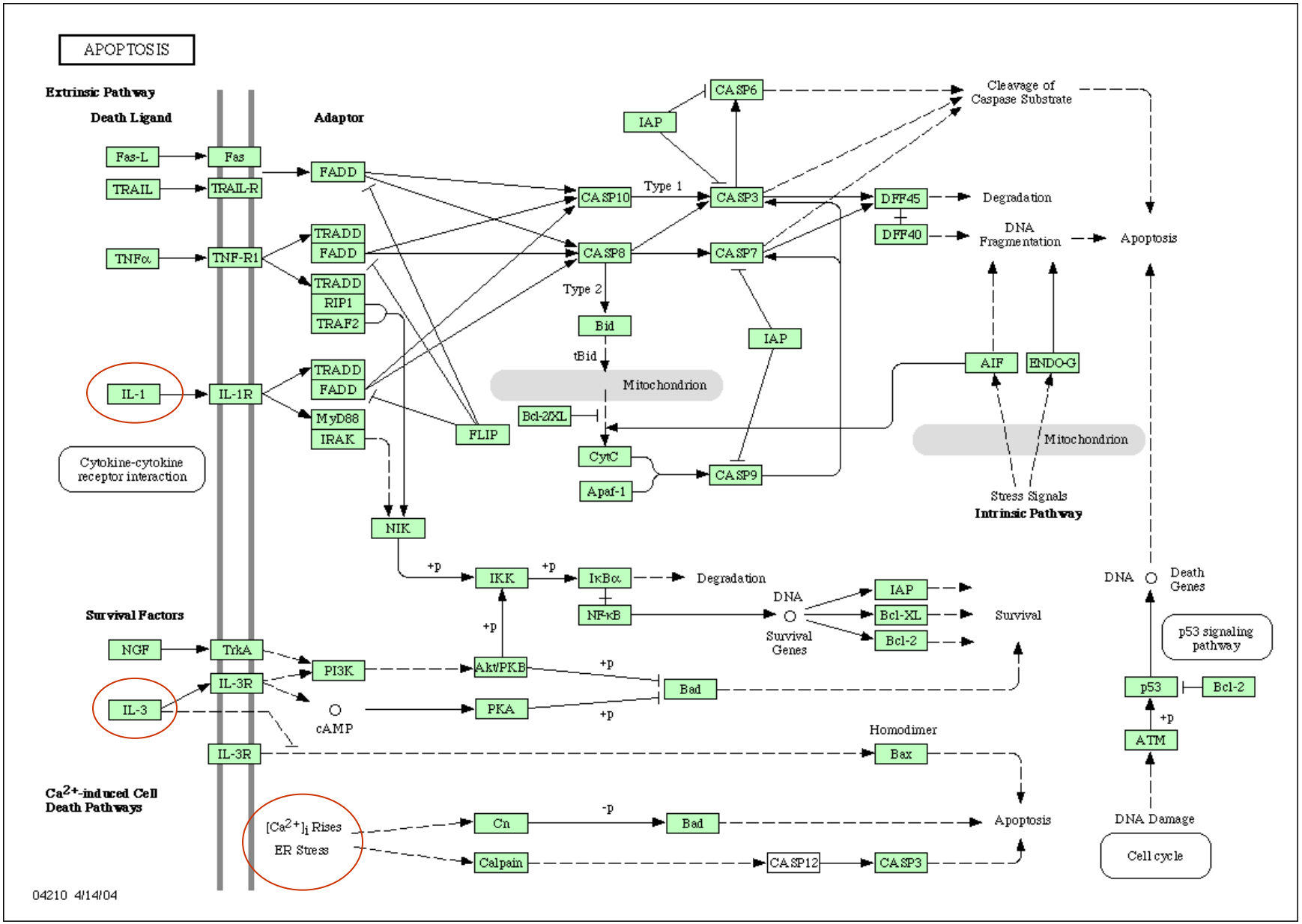
We try to understand this in the framework developed so far

Neuron-Astrocyte-Capillary System




Phosphatidylinositol signaling system
Focal Adhesion
PI(5)P
PI5K
2.7.1.149
PI(4,5)P2
PI(5)KP4K
PI(4)P5K
PIPK
Type1A, 1B PI3K
PTEN
2.7.1.153
PLC
PLC
3.1.3.36
IP5 phosphatase
Type1A PI3K
Phosphatidyl-1D-myo-inositol (PI)
PI4K
PI(4)P
PIP
PI(3,5)P2
PI(3,4,5)P3
I(1,3,4,6)P4
2.7.1.134
I(1,3,4,6)P4
2.7.1.140
I(1,3,4,5,6)P5
2.7.1.-
IP6
IP6P
PI(3)P5K
2.7.1.150
I(1,3)P2
3.1.3.64
I(1)P
3.1.3.25
I(1,3,4,5)P4
3.1.3.56
I(1,3,4)P3
3.1.3.57
I(3,4)P2
3.1.3.66
I(3)P
3.1.3.25
I
PTEN
3.1.3.64
Type1A, 1B, II PI3K
2.7.1.154
Membrane trafficking
IP3 3K
I(1,4,5)P3
3.1.3.56
I(1,4)P2
3.1.3.57
I(4)P
3.1.3.25
(IP3)
P3 5phosphatase
I(1,4)P2 1phosphatase
PLC
SHIP
Type1A,1B,II, III PI3K
2.7.1.137
PI(3)P
3.1.3.66
PI(3,4)P2
DG
2.7.1.107
PA
2.7.7.41
CDP-DG
DG kinase
PTEN
3.1.3.64
Membrane trafficking
IP4 phosphatase
Akt / Pkb survival signaling pathway
OH
Ca2+
IP3R
PKC
Calm
2.7.8.11
PI synthase
(CDP-DG:I transferase)
04070 4/8/05


CALCIUM SIGNALING PATHWAY
NCX
Na+
PMCA
Neurotransmitter, autacoid
GPCR
Gs
ADCY
cAMP
PKA
ER/SR
+p
PLN
SOC
Depletion of Ca2+ stores
SERCA
VOCs
CaV1
CaV2
CaV3
Membrane depolarization
Ca2+
RYR
Neurotransmitter, autacoid
ROC
Neurotransmitter, hormone, autacoid
GPCR
Gq
PLCδ
PLCβ
PLCγ
PLCε
PLCζ
Growth factor
PTK
TCR
BCR
Antigen
Sperm
cAMP
IP3
IP3R
DAG
?
ATP
CD38
NADH
cADPR
NAADP
NAADPR
?
SPHK
S1P
S1PR
MCU
Mitochondrion
NCX
VDAC
ANT
PPID
Na+
Ca2+
CALM
TnC
MLCK
PHK
Contraction
Metabolism
MAPK signaling pathway
Apoptosis
CaN
CAMK
Proliferation
Fertilization
Learning and memory
Long term potentiation
Long term depression
NOS
ADCY
PDE1
FAK2
IP3 3K
PKC
Other signaling pathways
Phosphatidylinositol signaling system
Exocytosis
Secretion
04020 9/26/06


APOPTOSIS
Extrinsic Pathway
Death Ligand
Adaptor
Fas-L
Fas
TRAIL
TRAIL-R
TNFα
TNF-R1
IL-1
IL-1R
Cytokine-cytokine receptor interaction
FADD
TRADD
RIP1
TRAF2
MyD88
IRAK
FLIP
NIK
IKK
IκBα
NF-κB
Degradation
DNA
Survival Genes
IAP
Bcl-XL
Bcl-2
Survival
Survival Factors
NGF
TrkA
IL-3R
IL-3
PI3K
Akt/PKB
PKA
cAMP
Bad
Homodimer
Bax
Ca2+-induced Cell Death Pathways
[Ca2+]i Rises
ER Stress
Cn
Calpain
-p
CASP12
CASP3
Apoptosis
CASP10
Type 1
CASP8
Type 2
Bid
tBid
Mitochondrion
Bcl-2/XL
CytC
Apaf-1
CASP9
CASP6
IAP
CASP3
CASP7
DFF45
DFF40
Degradation
DNA Fragmentation
Apoptosis
AIF
ENDO-G
Mitochondrion
Stress Signals
Intrinsic Pathway
Cleavage of Caspase Substrate
DNA
Death Genes
p53 signaling pathway
p53
Bcl-2
ATM
DNA Damage
Cell cycle
+p
04210 4/14/04

Failure Condition Analysis

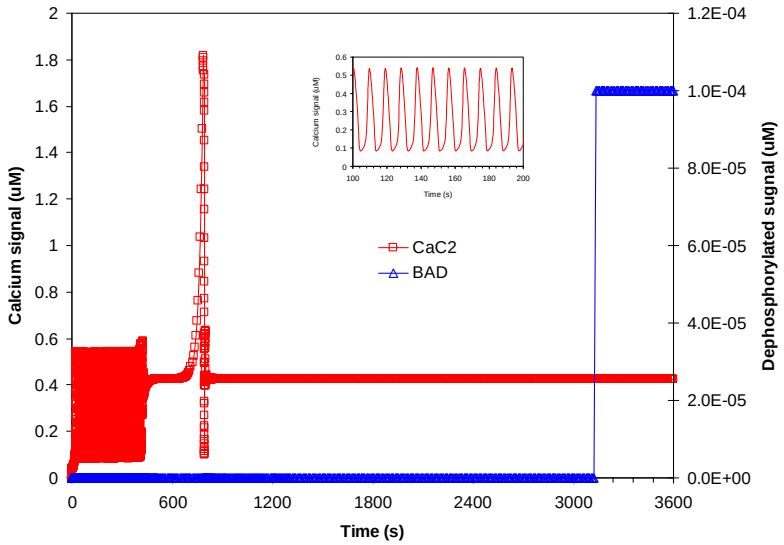
Material flow failure – robust response – safe

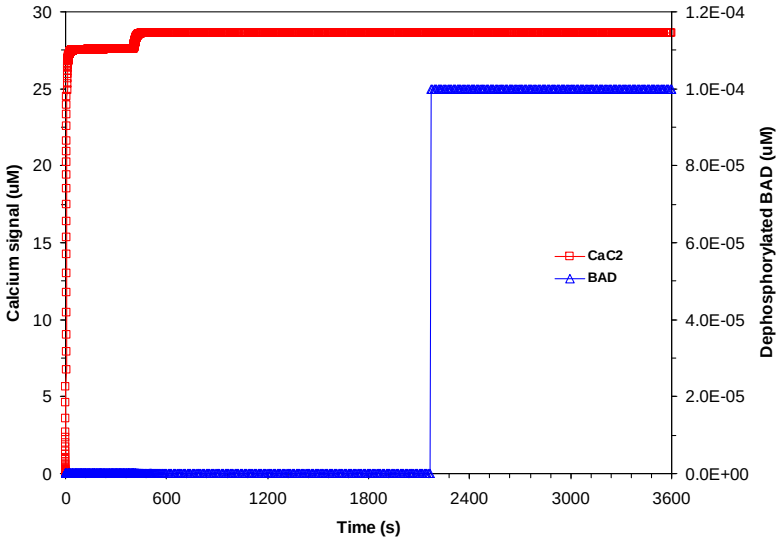
- Elevated blood glucose
- Elevated blood glutamine

Signaling Failure

- Changes in binding affinity – robust response – safe
- Changes in CICR (Ca induced Ca release) – sensitive – can cause a disorder

CICR Failure Analysis





A sustained Ca2+ signal triggers dephosphorylation of BAD. The level of the signal influences the time it takes to trigger. Once BAD is triggered apoptosis sets in.

SUMMARY

Systems Biology is an emerging area with the potential of making a significant contribution to human life

- Drug targeting
- Drug designing
- Elucidating basic principles
- Prediction of disease conditions