Lecture presented to the Workshop on Stochastic Modelling of Biological Networks
Organized by Professor Xuerong Mao, University of Strathclyde
14 September 2010

Networks, noise and nodes

- Pat Heslop-Harrison
- With Declan Bates, Kwang-Hyun Cho (and lab), Jongrae Kim, Najl Valeyev, Ian Postlethwaite, Jung-Su Kim

Networks, noise and nodes

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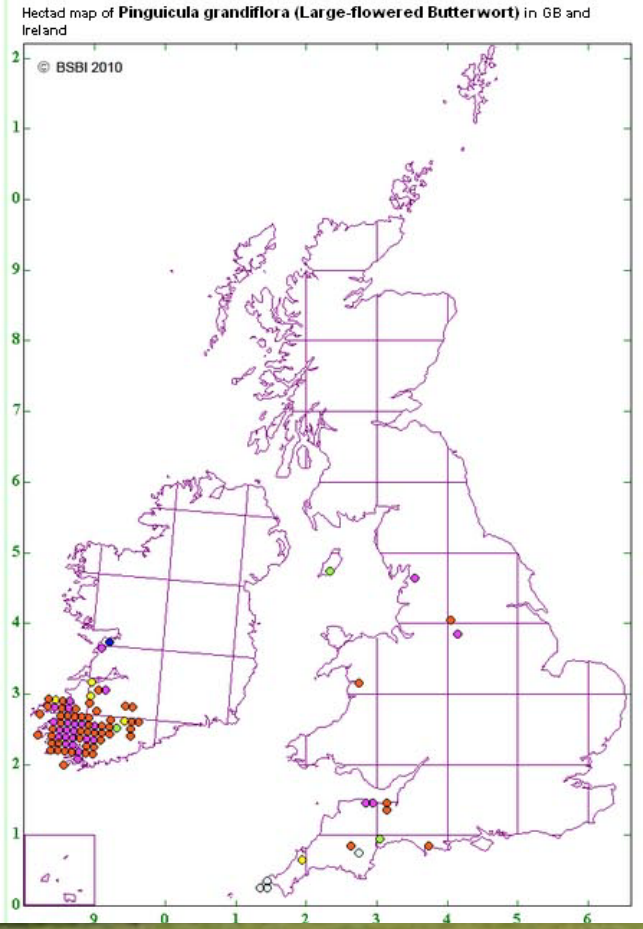
Hectad map of **Pinguicula grandiflora (Large-flowered Butterwort)** in GB and Ireland

Hectad map of **Pinguicula vulgaris (Common Butterwort)** in GB and Ireland

After Y Heslop-Harrison. 2004. Pinguicual. J. Ecol. http://www.blackwell-synergy.com/oper


Hectad map of **Pinguicula grandiflora (Large-flowered Butterwort)** in GB and Ireland
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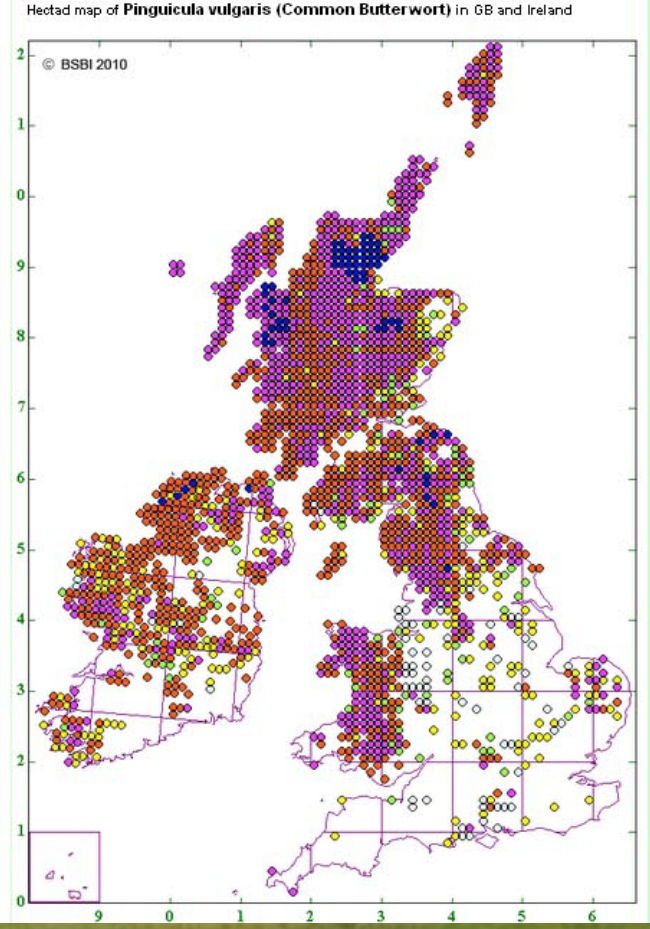
Hectad map of **Pinguicula vulgaris (Common Butterwort)** in GB and Ireland
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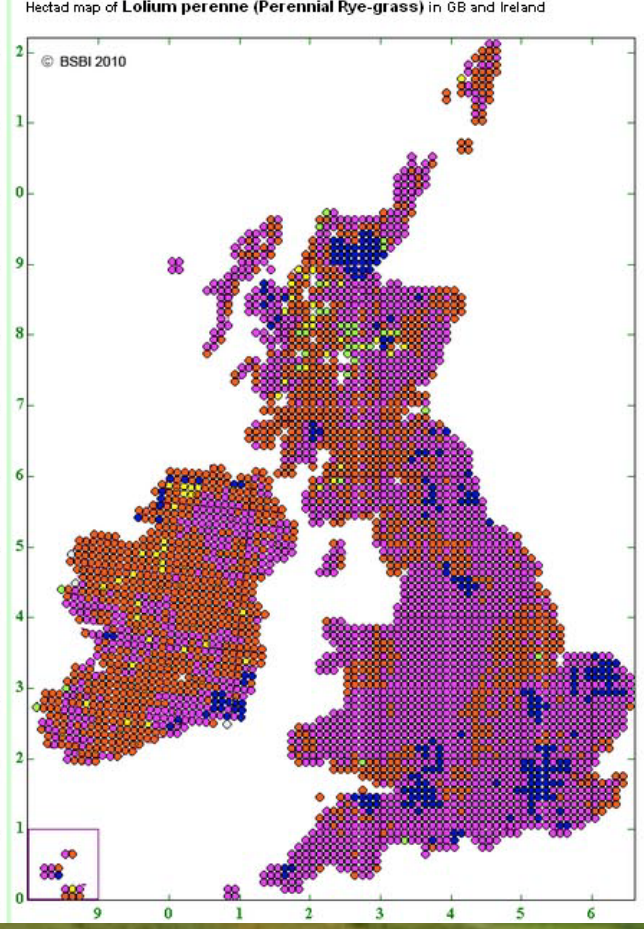
Hectad map of **Lolium perenne (Perennial Rye-grass)** in GB and Ireland
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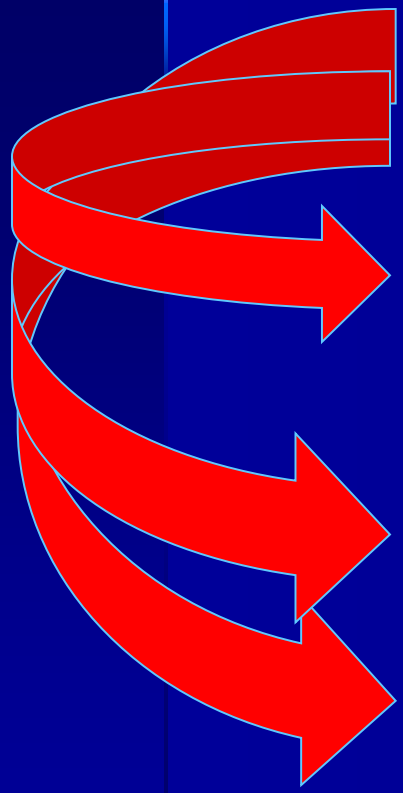
- Without understanding nodes, networks and noise …
- There will be no consequences!

What is needed to study

- Data
- Experiments or observations
- Models
- Testing

What is needed to study



- Data
- Experiments or observations
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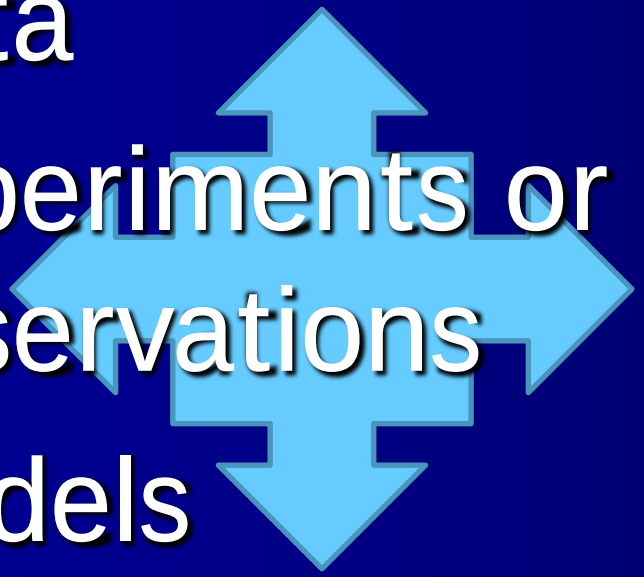
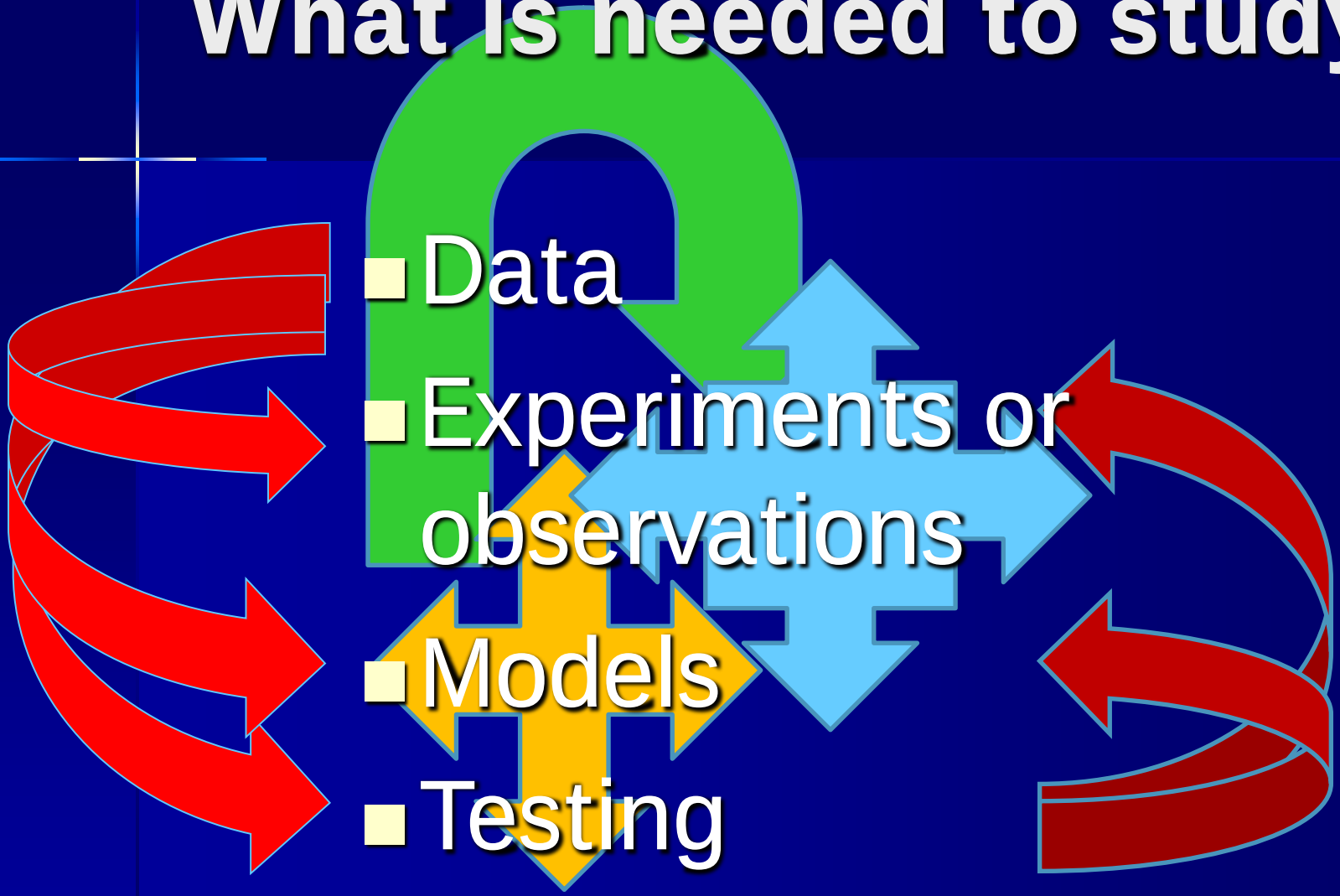
- Testing

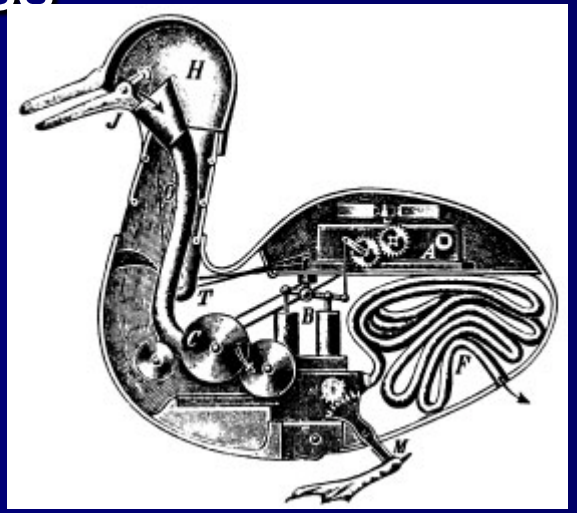


What is needed to study!



- Data
- Experiments or observations
- Models
- Testing

- The big picture
- Research context
- Noise,
- Signalling,
- Switching,
- Oscillations,
- Functionality and robustness
- Genetics and genomics
- Evolution
- … Simplification



Canard Digérateur Duck of Vaucanson 1739

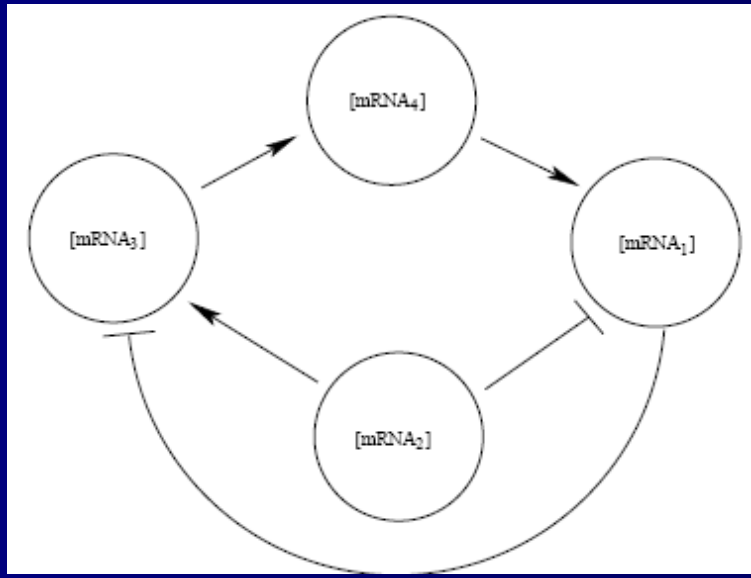
Noise and variation in responses

- Measurement noise
- Continuous variables or discrete

- Stochastic processes
- Final state depends on controlled response and random element

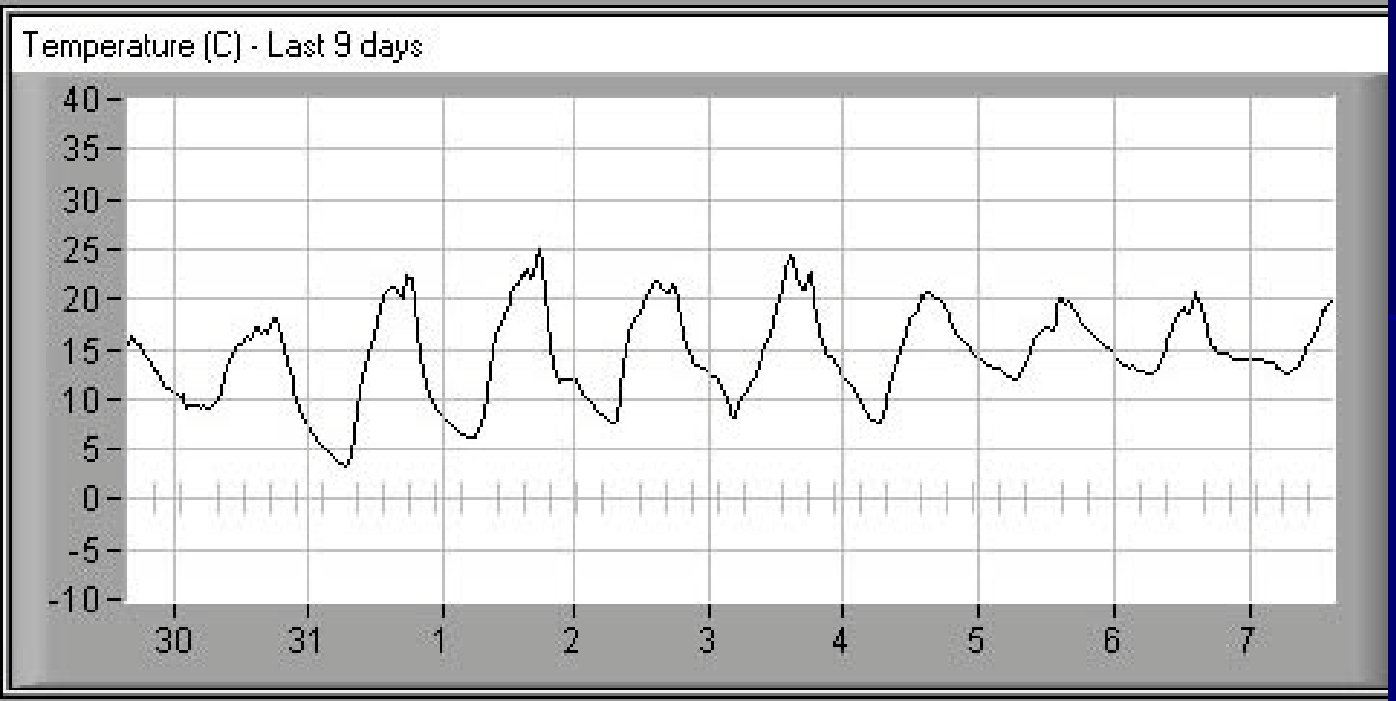
Interactions in noisy experimental data

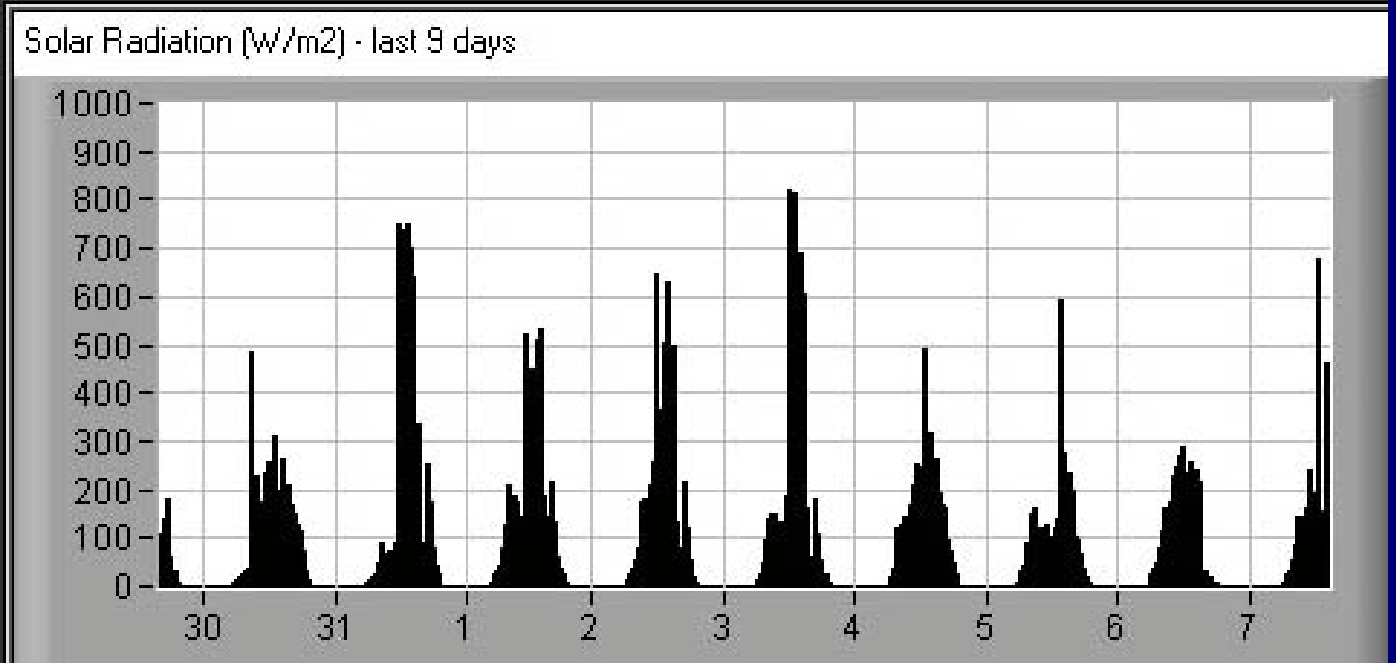
- For reliable identification and modelling of biochemical networks and assisting experimental design
- Constrained Total Least Squares (CTLS)
  noise components correlated
- Approach reduces errors in estimates of interactions



Jongrae Kim et al. Least-squares methods for identifying biochemical regulatory networks from noisy measurements. BMC Bioinformatics 8:8 2007

www.oadbyweather.com






08 September 2010


www.die.net/earth/
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Noise and variation in responses

- What is measured?

- Dobzhansky: “Nothing makes sense except in the light of evolution”

Noise and variation in responses

- Why is the information used?
- Final state depends on controlled response and random element

Life on the edge …

- Verge of stability for fire with 20% oxygen

Flooding Ann Bot 2009: 103: 137ff

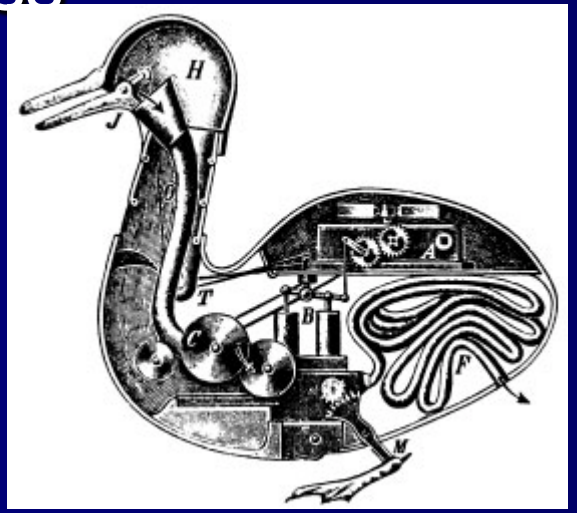
Water – quality and quantity

- Temperature – too hot or cold

ABIOTIC FACTORS

With huge amount of regulation needed

- The big picture
- Research context
- Noise,
- Signalling,
- Switching,
- Oscillations,
- functionality and robustness
- Genetics and genomics
- Evolution
- … Simplification



Canard Digérateur Duck of Vaucanson 1739

Renewal and repair

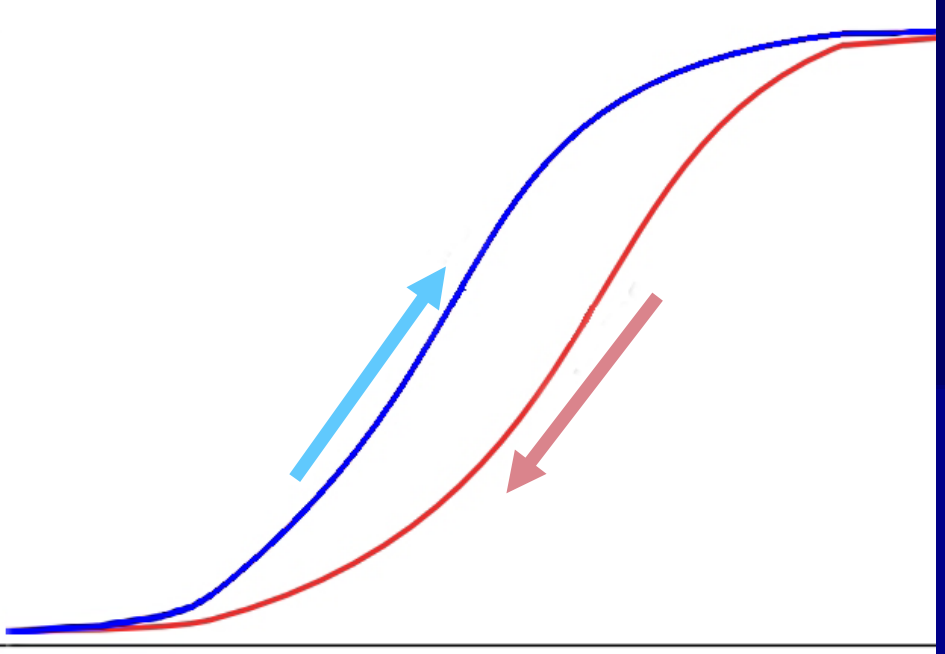
- Amazingly short lifespans
- Most organisms live a few days
- But a few live a century
- Lifespan is species specific

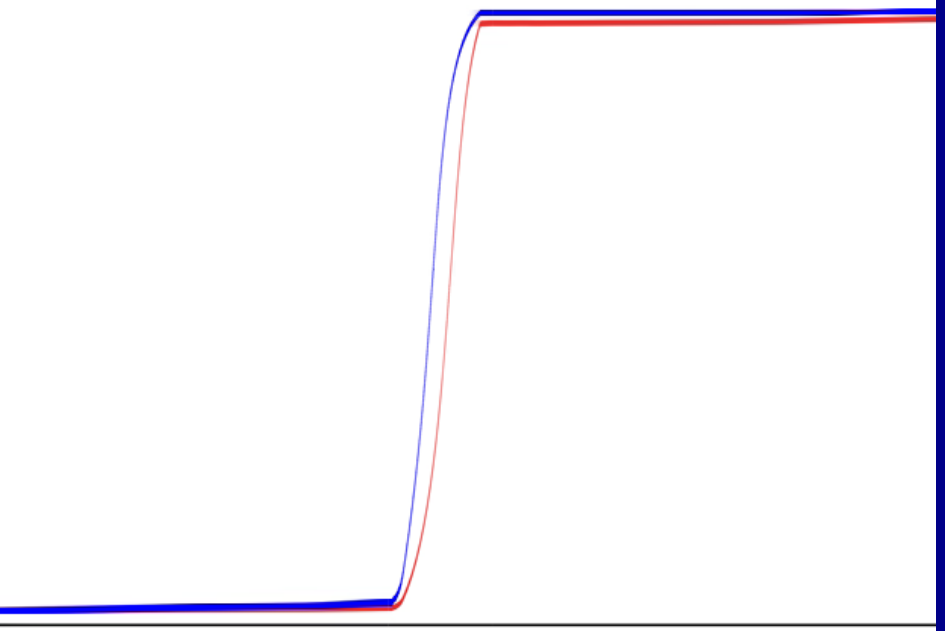
Instability means continuous renewal: repair, start again

Renewal and repair

- Energy balance
- Renewal and repair needs inputs
- Comparisons
  - What ‘should’ be there
- Absolute measurement
  - “It needs renewing”
  - “It will soon fail”

Instability means continuous renewal: repair, start again





Switching

- Rate
- Hysteresis

- X – stimulus (light, temperature, force)
- Y – response (movement, sweating, extension)

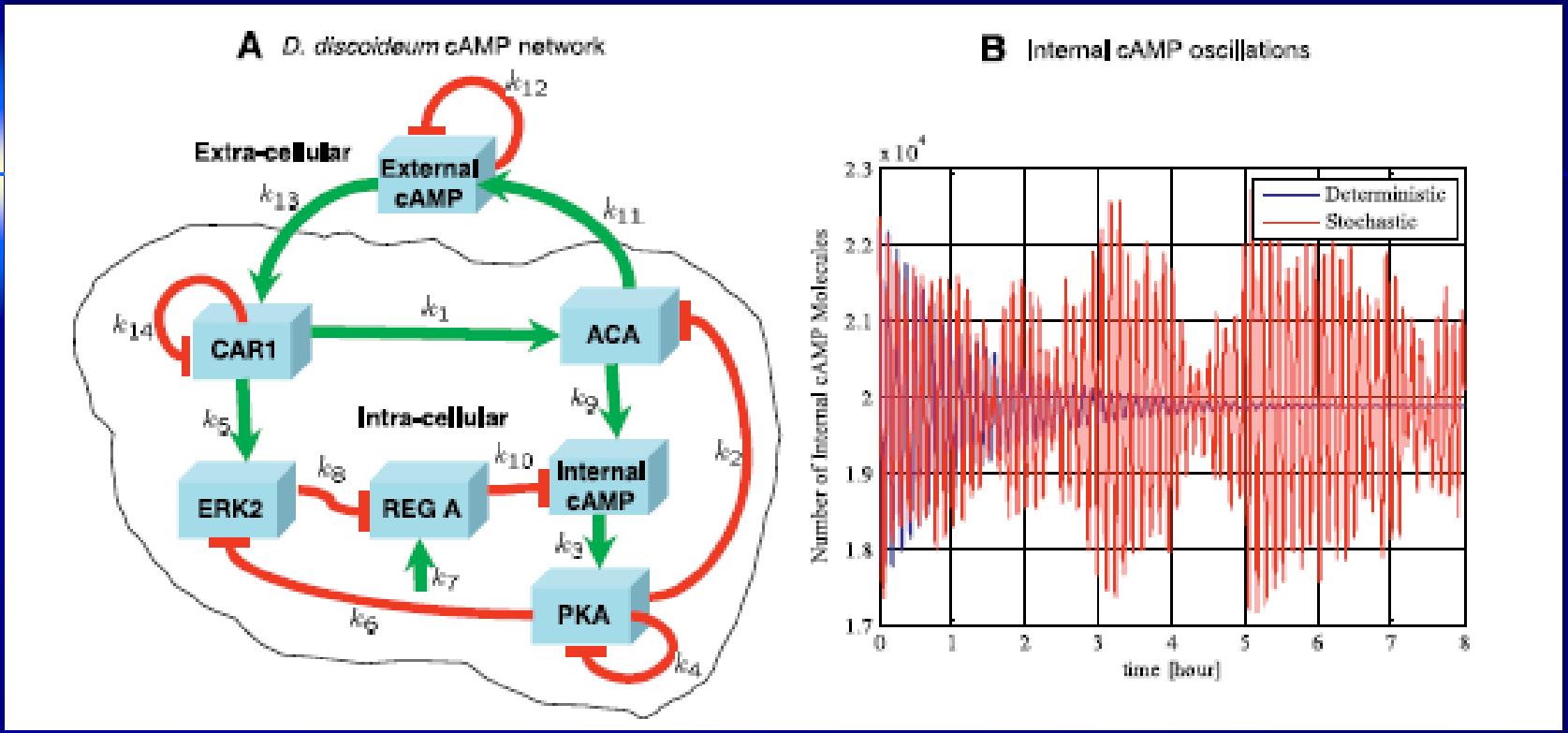
Oscillations

- Related to instability
- Many biological processes are oscillating and many control systems are in place to control these
- Many aspects of development require reiteration of processes
- Feedforward is important: changes because of what is predicted to be going to happen

Oscillations: driven and driving

Stochastic variations give rise to possibility for accurate and variable control

Oscillations: noise and stability



- Stochastic fluctuations
  - preserve stable oscillations
  - ensure robustness of the oscillations to cell-to-cell variations
- Robustness analysis requires stochastic simulation

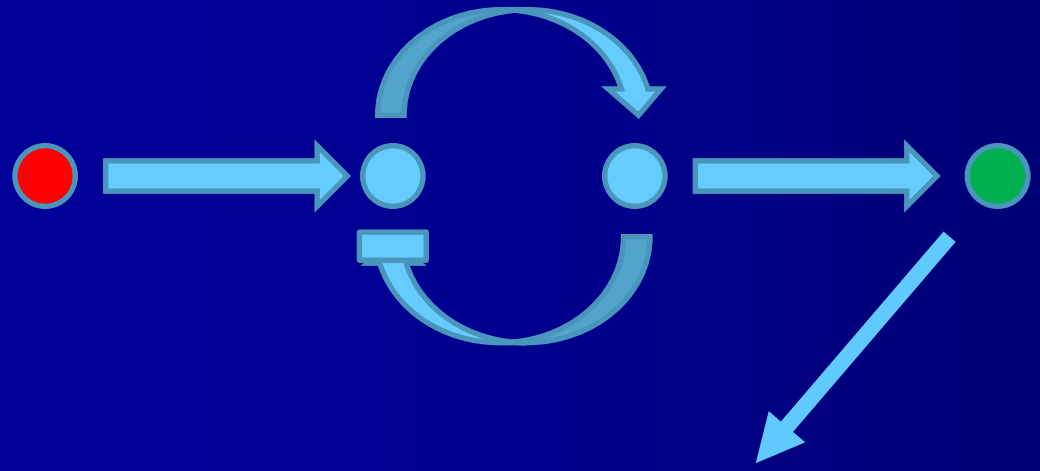
JongRae Kim et al. Stochastic noise and synchronisation during Dictyostelium aggregation make cAMP oscillations robust. PLoS Computational Biology 2007

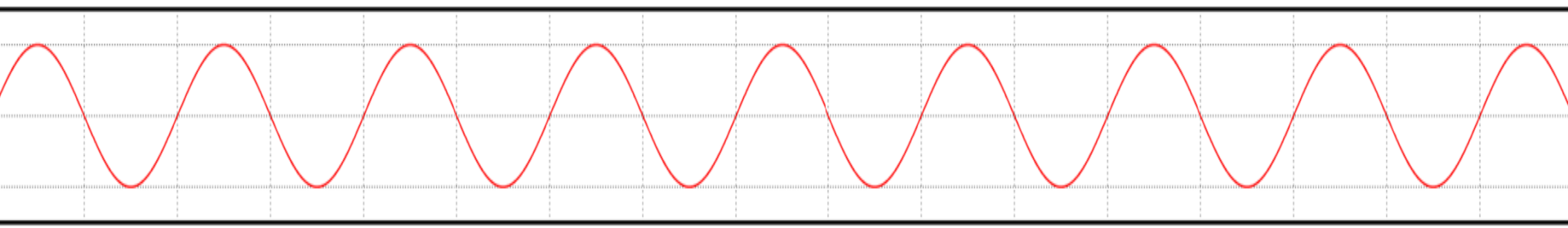
Regulation of oscillations

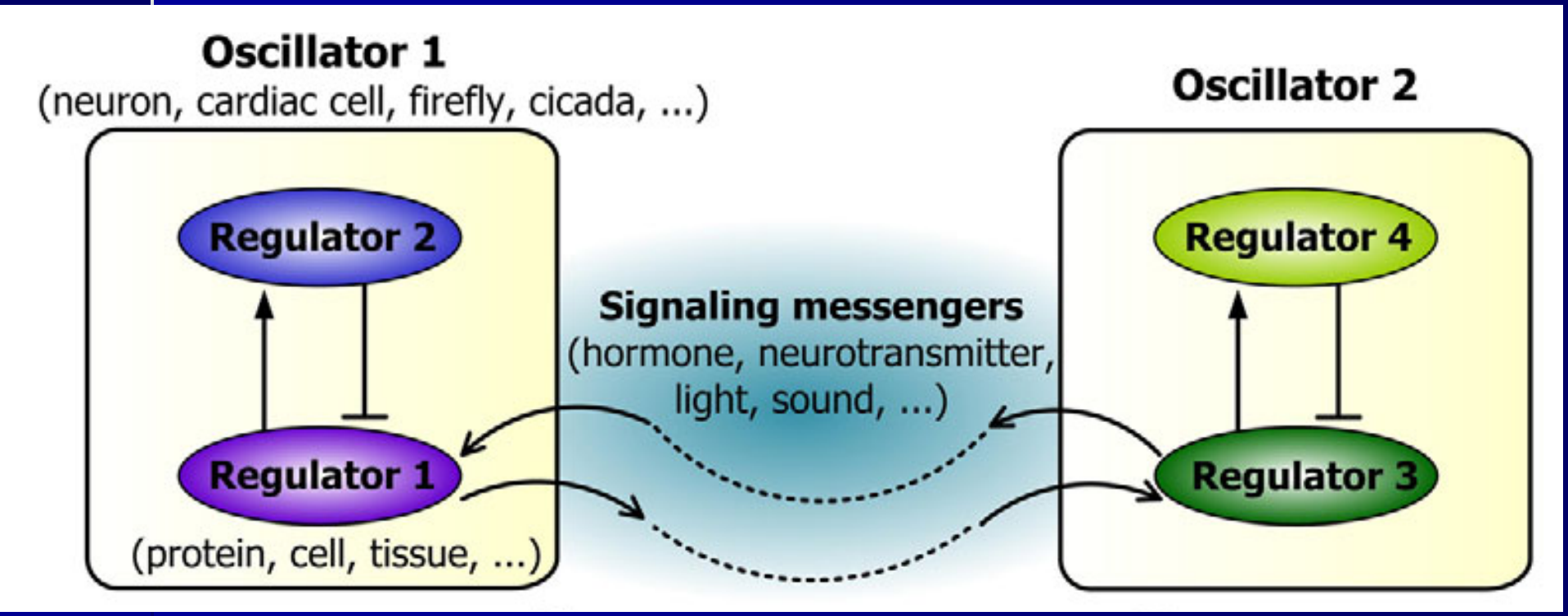
- External master regulation
  - Tidal (12 hr/1 month)
  - Circadian (1 day)
  - Seasonal (temperature/daylength)
- 30% of genes show diurnal variation in expression

Regulation of oscillations

- Synchronization without external regulators

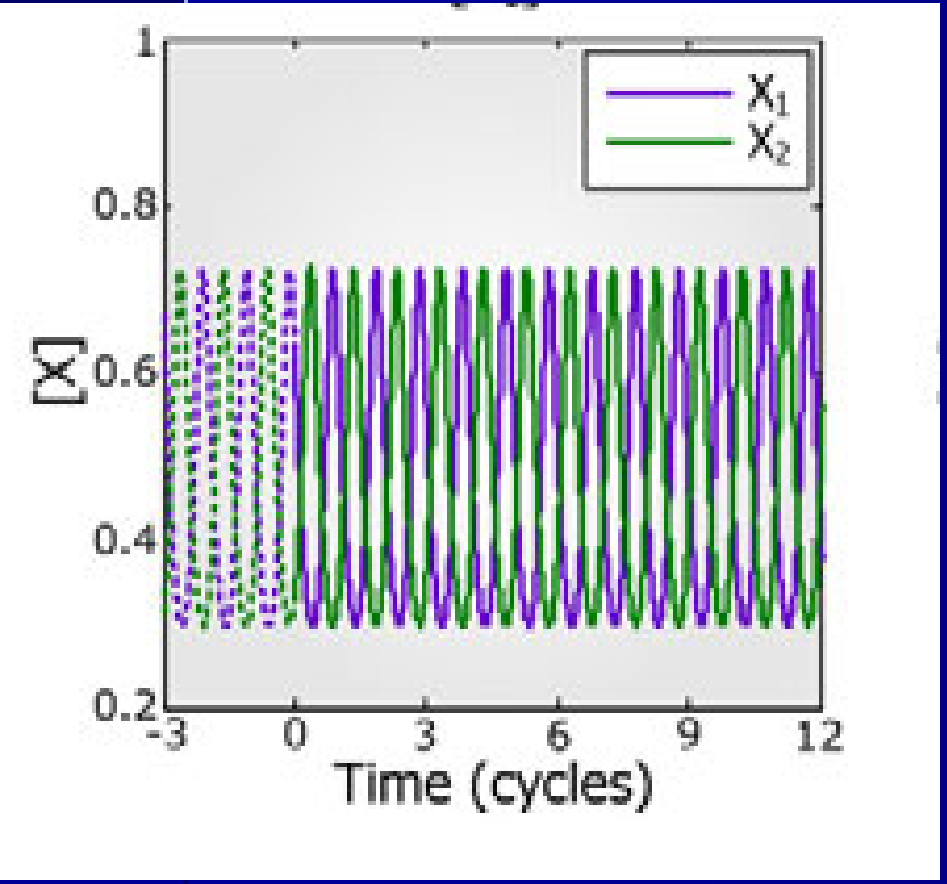


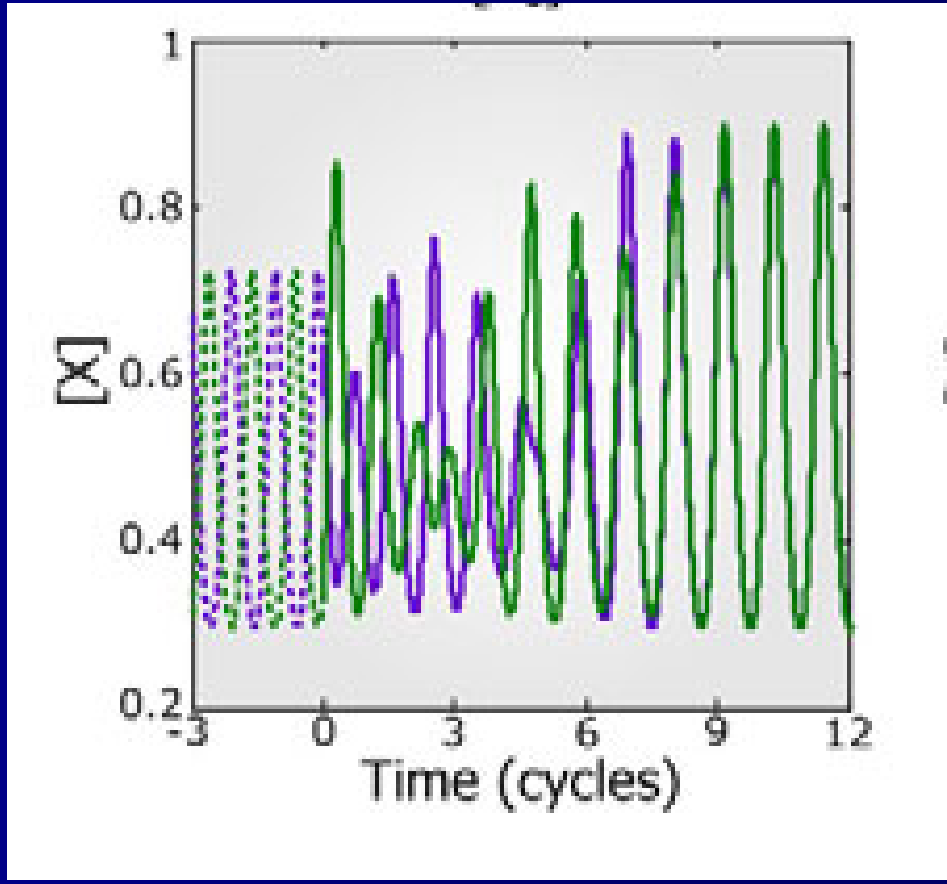


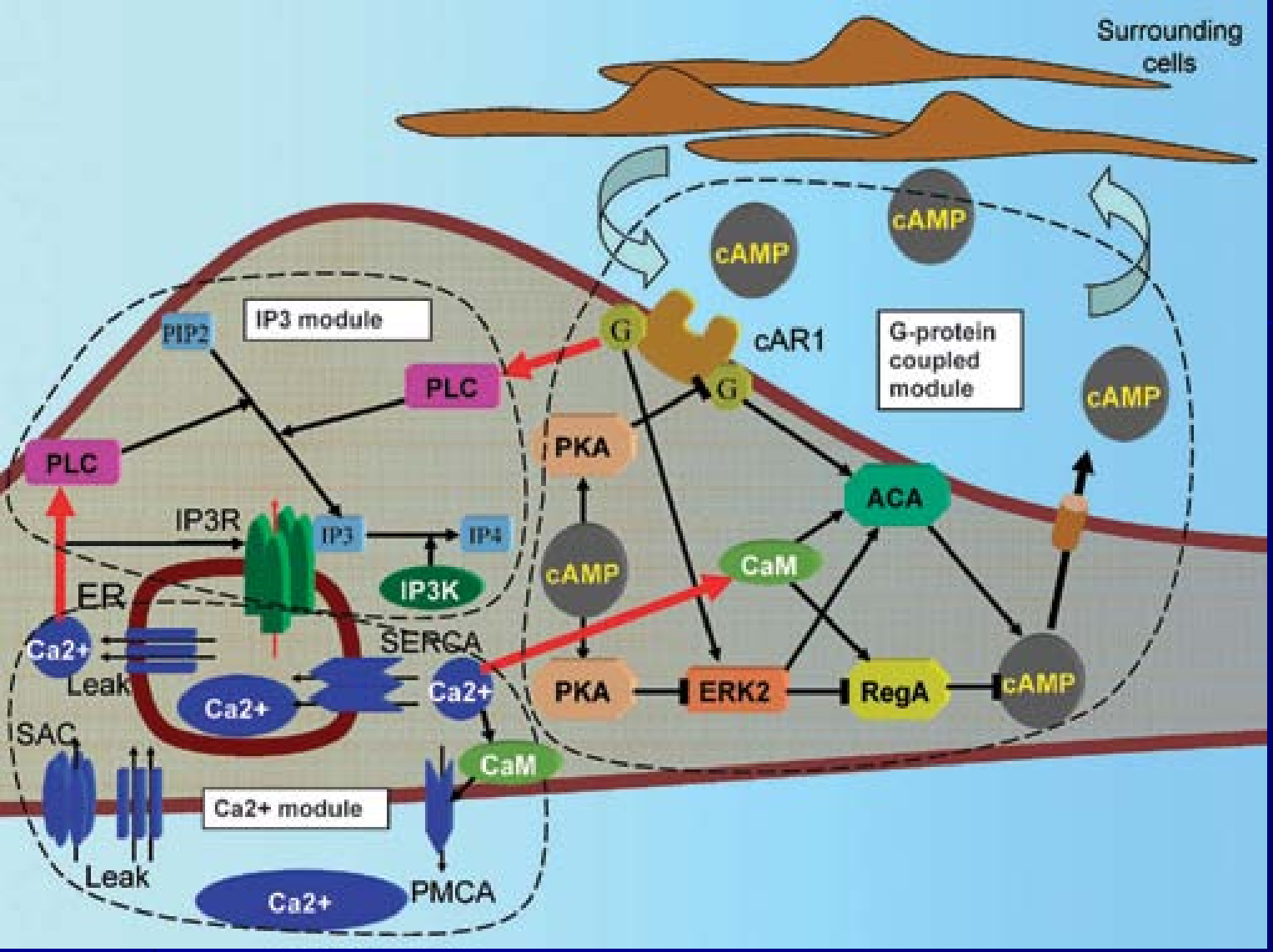


Jeong-Rae Kim, Kwang-Hyun Cho. J Cell Sci 2010

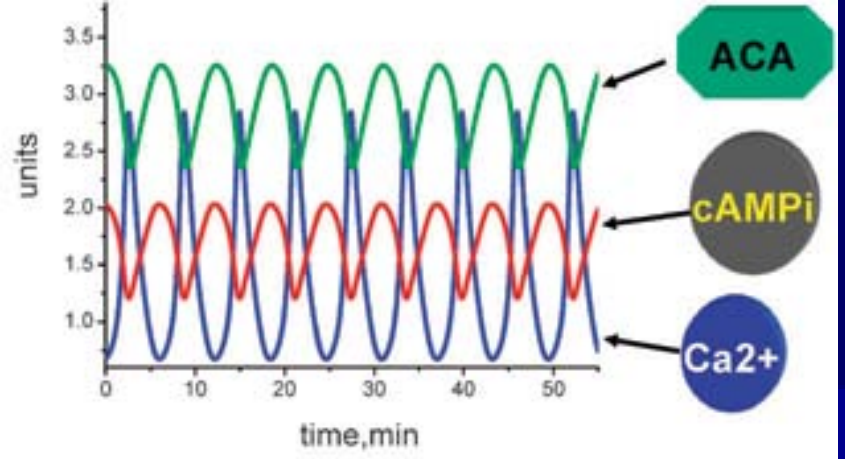
Weak Stronger Coupling

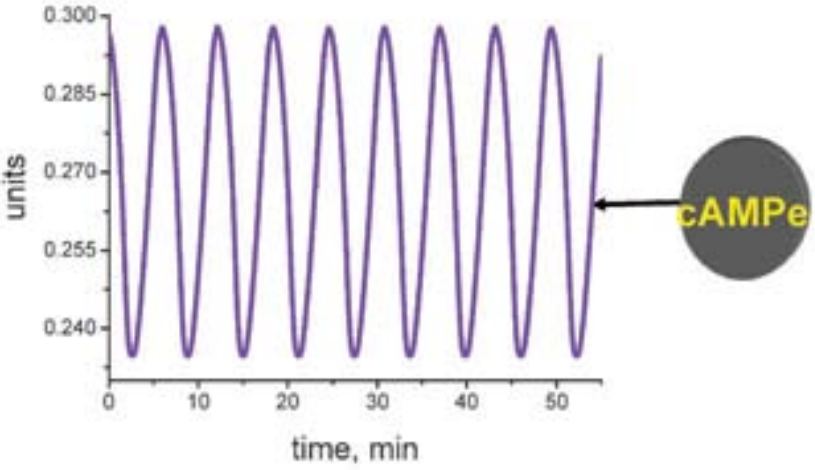


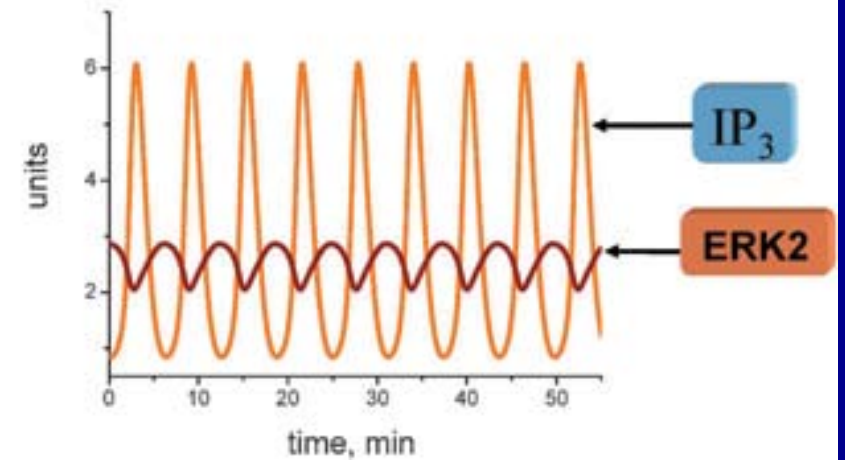




- Dynamic interactions between calcium, IP3 and G protein-dependent modules
- Valeyev et al. Mol Biosyst 2009 5: 612

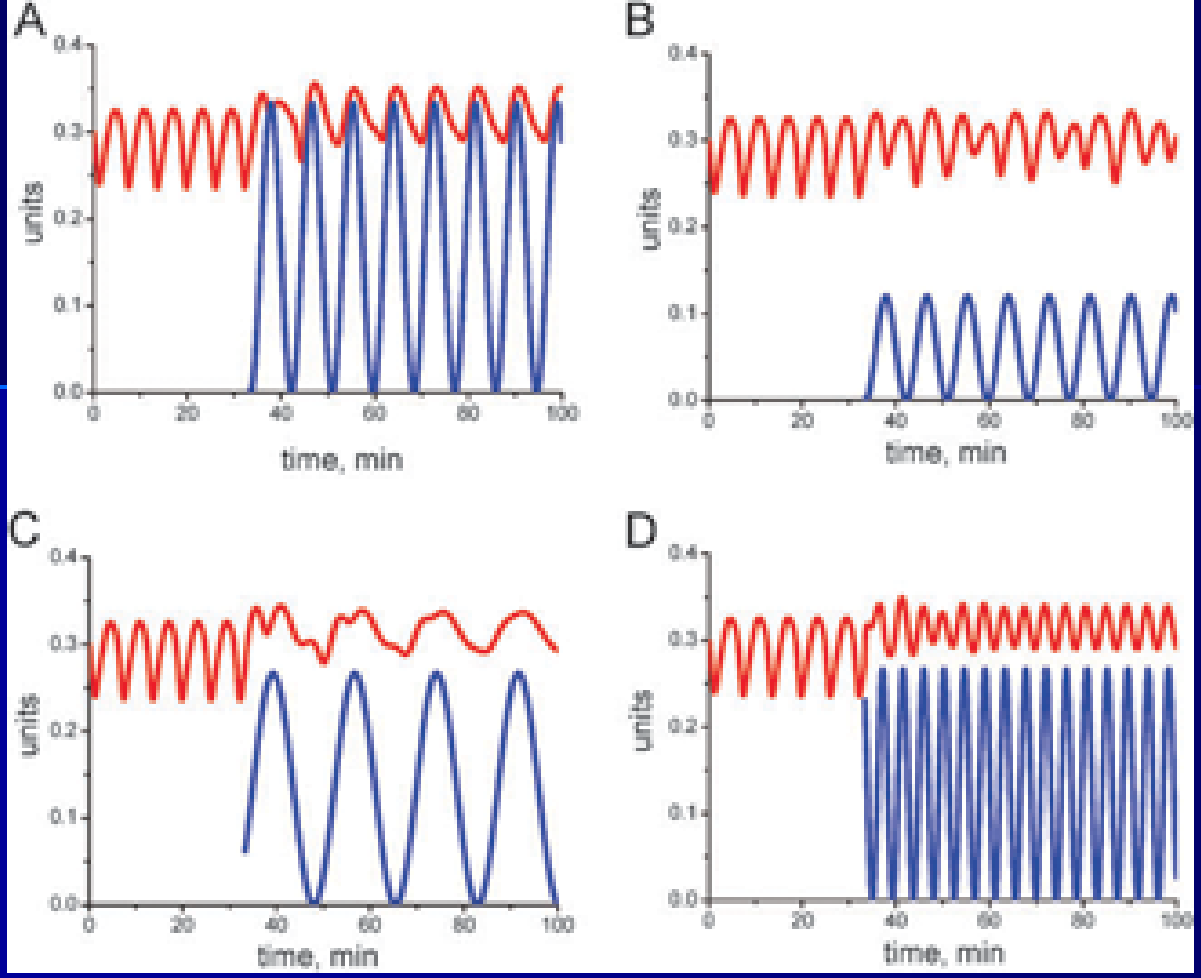






- Stable cAMP oscillations in the cells with other molecules/ions

Valeyev et al. Mol Biosyst 2009



- Entrainment of a cell by surrounding cells:
- Individual cells synchronized/oscillate in phase
- Regardless of frequency, some effect of [cAMP]

Valeyev et al. Mol Biosyst 2009

Robustness: remarkable levels given instability ...

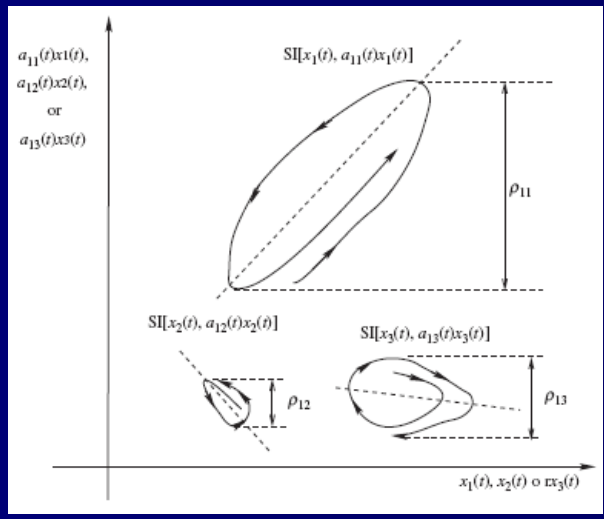
- Hypersensitive response controlled ...

Robustness: remarkable levels given instability … But not always

- **Hypersensitive response controlled … Or**
- **Cytokine storm**
- immune reaction with a positive feedback loop between cytokines and immune cells
- Implicated in human deaths
  - SARS 2003
  - bird flu H5N1
  - **TGN1412** immunomodulatory drug intended for chronic lymphocytic leukemia (B-CLL) and rheumatism

Non-linear interactions

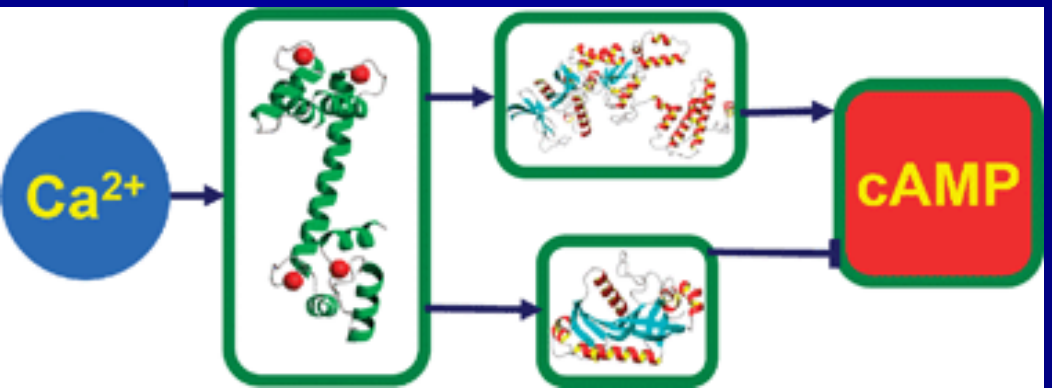
- "Stable instability": robust but oscillating is a feature of biomolecular networks
- Challenges
  - biological measurement
    - time-series profiles limited
  - no stable steady state
  - non-linear network interactions



Jongrae Kim et al. Linear time-varying models can reveal non-linear interactions of biomolecular regulatory networks using multiple time-series data. Bioinformatics

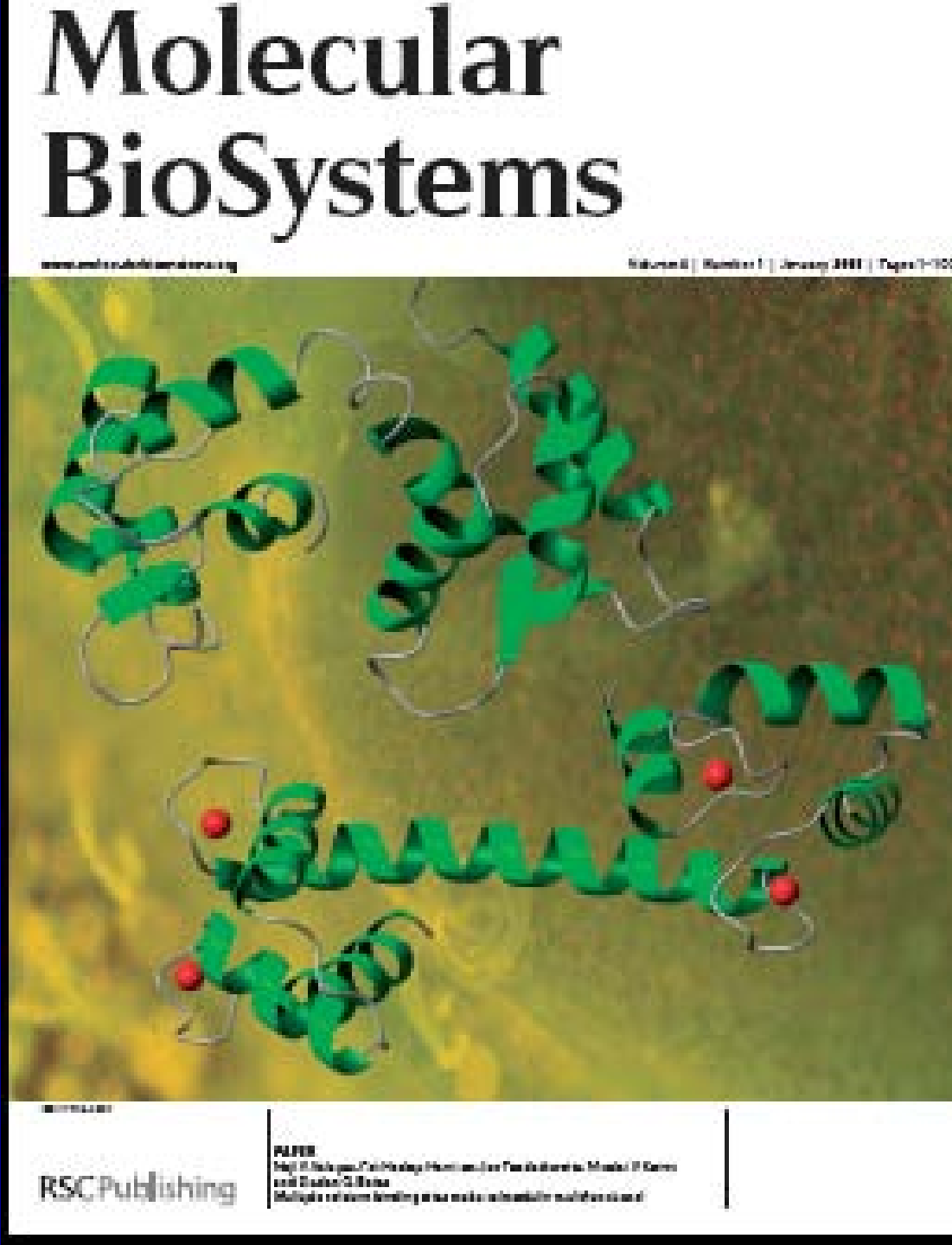
Function and multifunction

- How many genes are there?
- 1990s: perhaps 100,000 in human
- 2000: 25,000
- How does this give the range of functions and control?

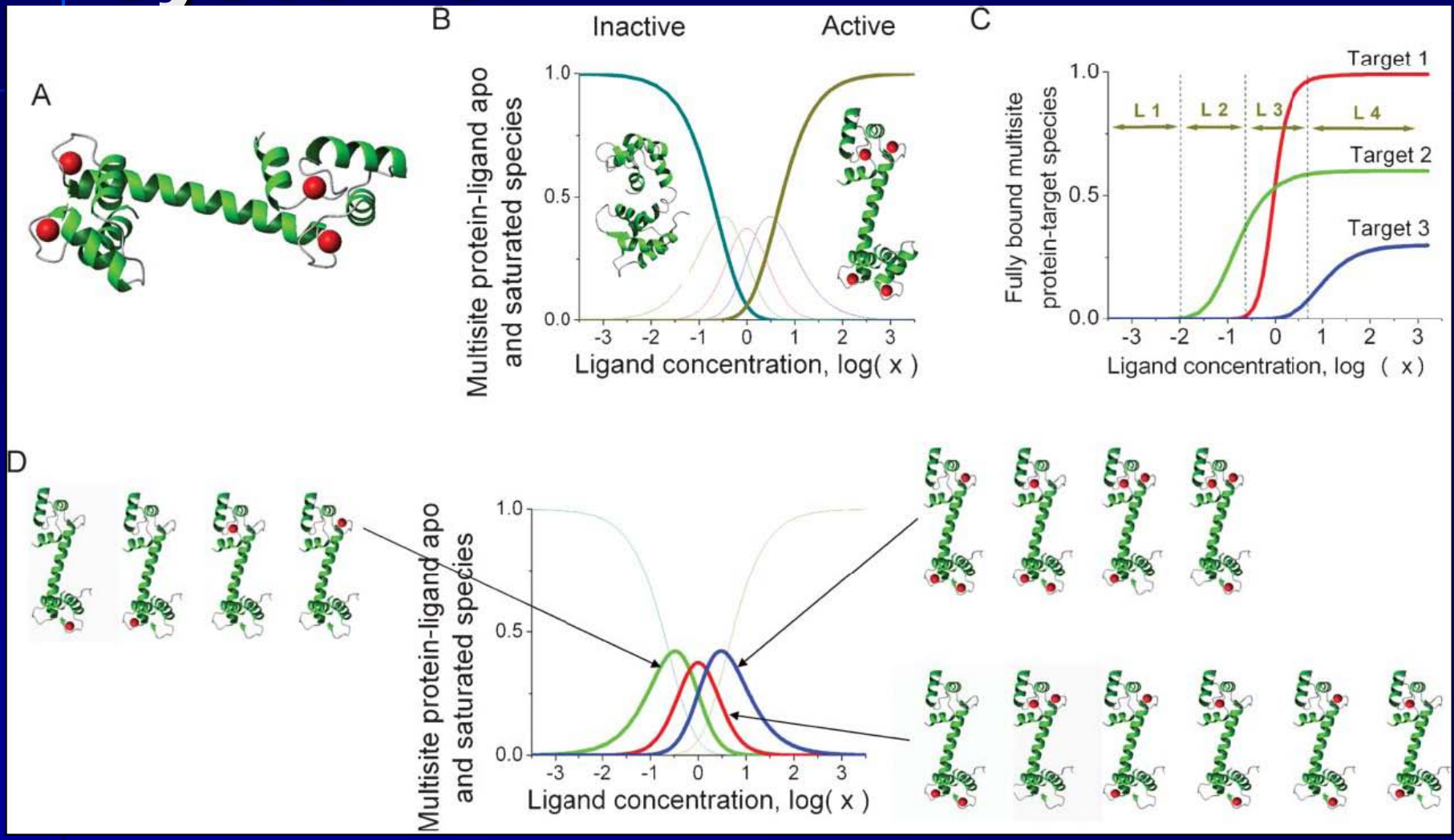


Najl Valeyev

- Ligand–multisite protein interactions selectively regulate the activities of multiple protein targets



Calmodulin: 30 regulated systems!



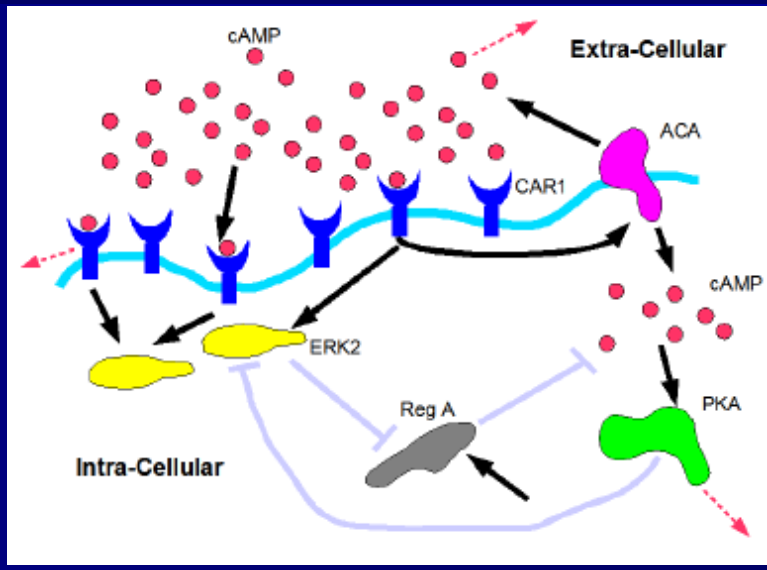
Multisite protein-dependent selective regulation is enabled

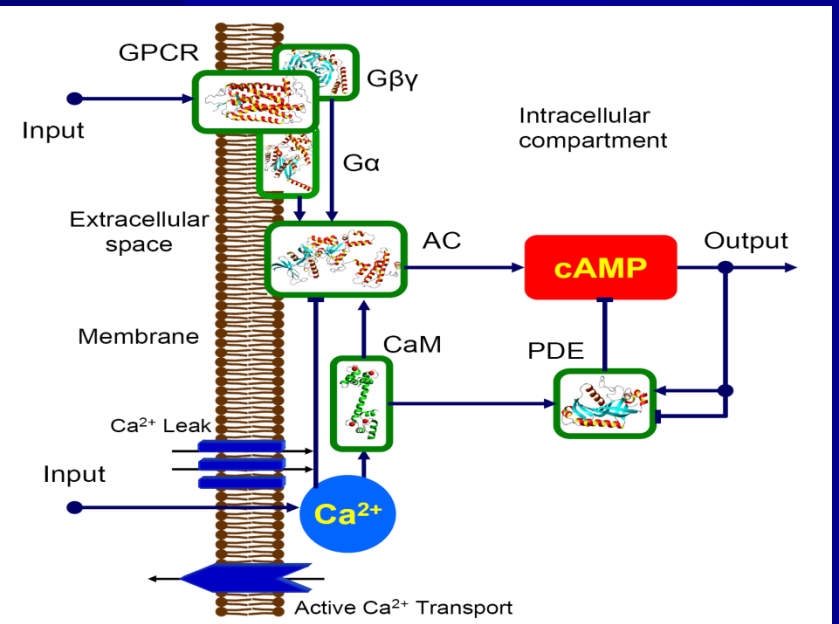
Duplication (and redundancy)

- Most plants and animals:
  - One complete set from mother, one complete set from father
- When it does not work, there are significant consequences
  - Men only have one X chromosome from their mother
  - 30% are colour-blind to some extent

Modularity and spatial locations – compartments and diffusion

- Diffusion volume and receptor numbers must be accounted for
  - Jongrae Kim et al. IFAC

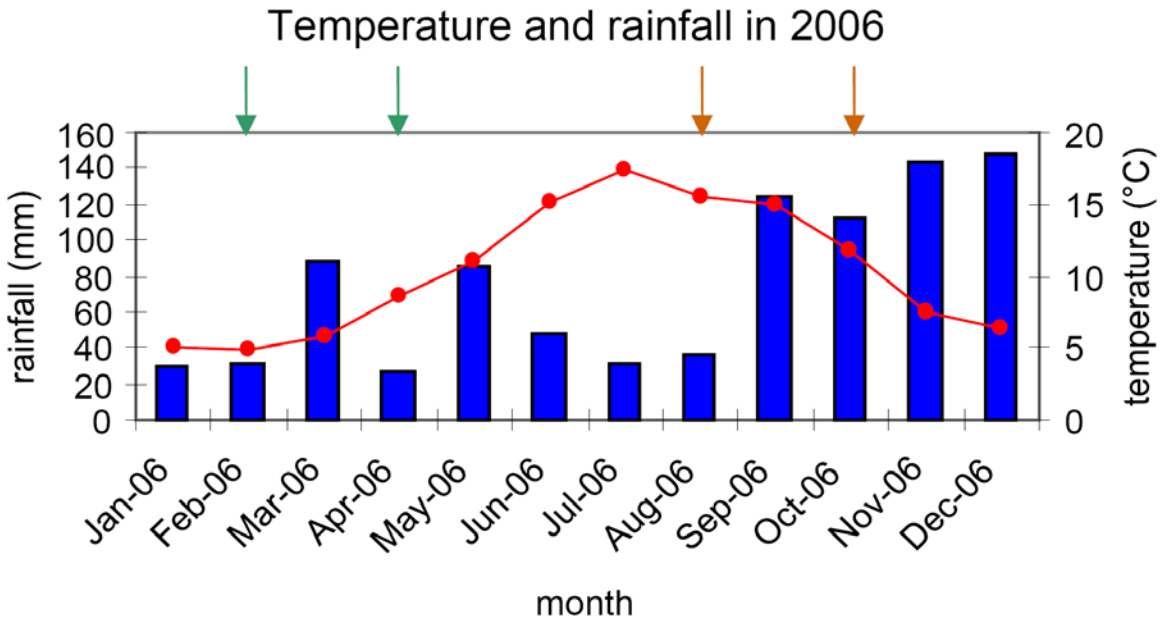


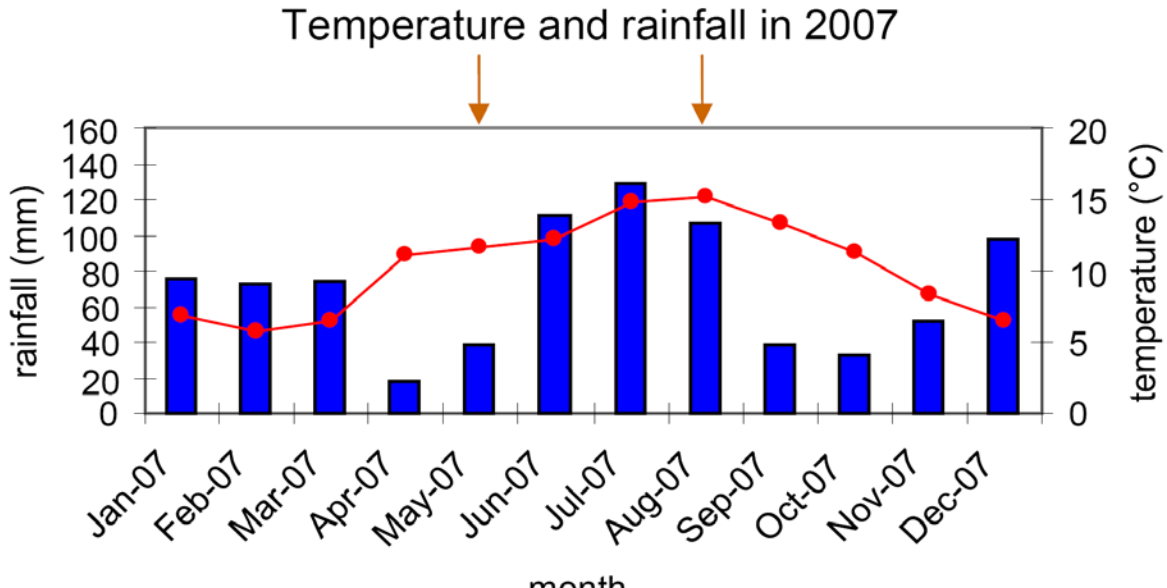


- Cross-talk can alter behaviour wildly
  - Valeyev 2009 Molecular Biosystems
- Cell migrations: animals and fungi

QTL – Quantitative Trait Loci

- Control of continuously varying characters
- Height, weight, yield





- Formidable genetic and environmental interactions
  - Anhalt, Barth, HH
  - 2009

- Formidable genetic and environmental interactions

Genetics involving AA and aa

AA, Aa and aa phenotype
Tall, medium and short

Involving AA, aa, BB and bb

AABB	AABb	AAbb
AaBB	AaBb	Aabb
aaBB	aaBb	aabb

tall ... 10 intermediates ... short

- Anhalt, Barth, HH 2009

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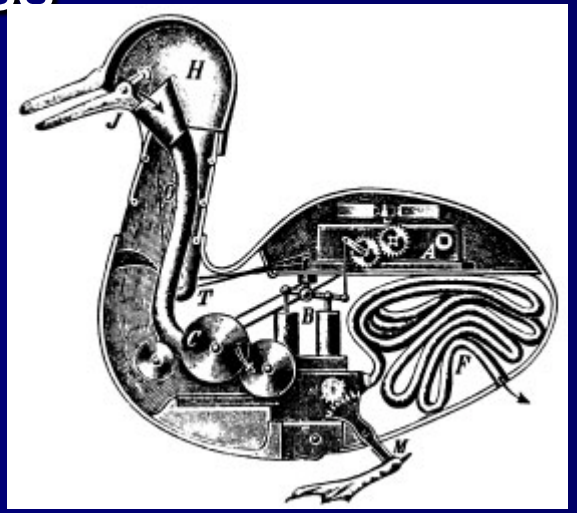
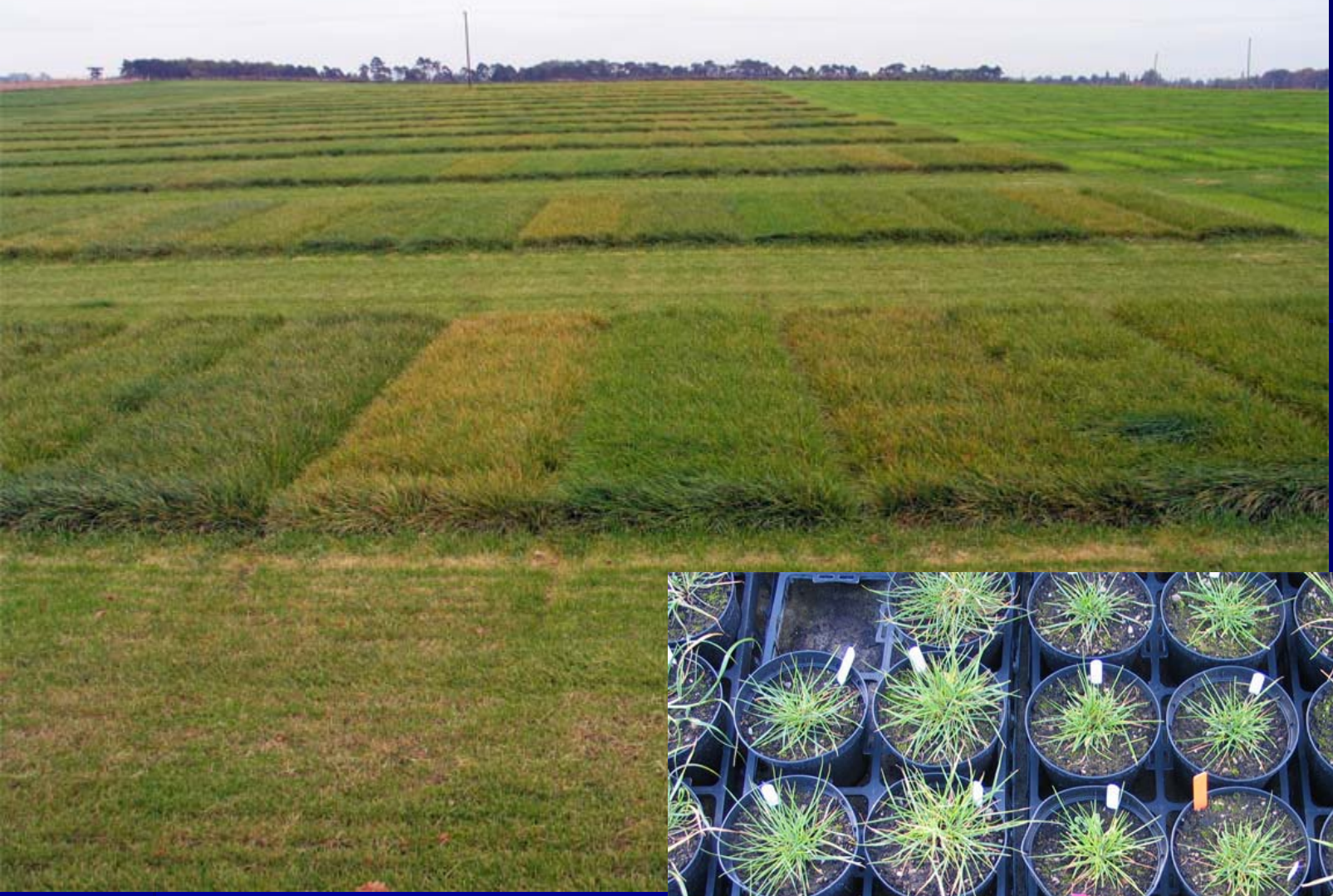


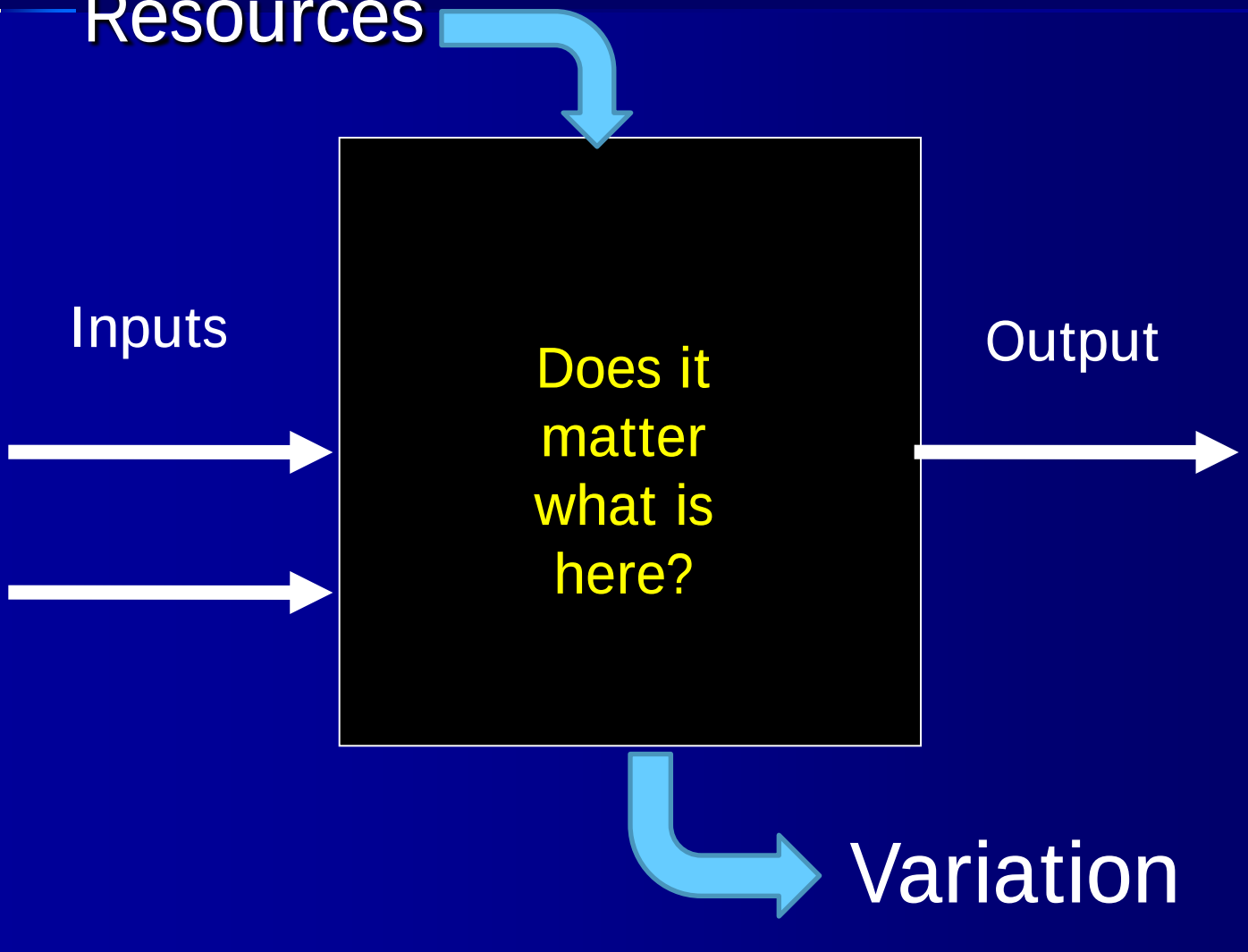
Canard Digérateur Duck of Vaucanson 1739


Inputs
Does it matter what is here?
Output



Anhalt, Barth et al. Segregation distortion in Lolium: evidence for genetic effects. Theoretcial & Applied Genetics 2008

Decisions and Memory



Death by Powerpoint, Internet Science Nerds, and #Solo10

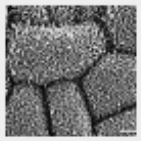
Lord Rees avoids Death by Powerpoint at #ScLo10. Photo (cc) Team Mendeley. As the undergraduates I teach will testify, I've railed many times against 'Death by Powerpoint'. Somewhat amazingly, a few talks at Solo10 did combine this decidedly 21st century phenomenon with mediaeval techniques to create a new level of torture, 'Hung, Drawn and Quartered by

More

Hormones and sugar network signalling in seeds

SEP 13TH Posted by Alex in ContentSnapshots | Edit

Hormones and sugar network signalling in seeds
Endospermic legumes are abundant in tropical forests and their establishment is closely related to



Nanotechnology and self-cleaning from plant leaf surfaces

SEP 10TH Posted by EditorPatHeslopHarrison in Life | Edit

SEARCH AOB SITES WITH GOOGLE

› Articles (3)

RESEARCH BLOGGING

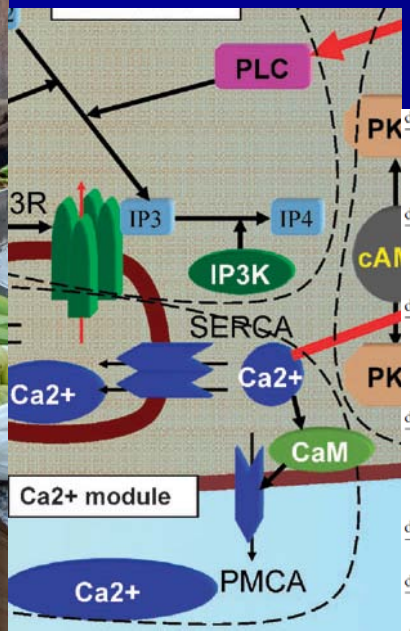
- Feeding Your Internal Ecosystem
- Falling Waters
- Epigenetic Memories


www.die.net/earth/
08 September 2010

United Nations Millennium Development Goals

- Goal 1 – Eradicate extreme poverty and hunger
- Goal 2 – Achieve universal primary education
- Goal 3 – Promote gender equity and empower women
- Goal 4 – Reduce child mortality
- Goal 5 – Improve maternal health
- Goal 6- Combat HIV/AIDS, malaria and other diseases
- Goal 7 - Ensure environmental sustainability
- Goal 8 - Develop a global partnership for development

- “Biochemistry explains biology”
- “Chemistry explains biochemistry”
- “Physics explains chemistry”
- “Mathematics explains physics”



$$\frac{d(ca_i^{2+})}{dt} = a_1 \cdot \left(\psi_i - 0.5 \cdot \ln\left(\frac{ca_{out}^{2+}}{ca_i^{2+}}\right)\right) - a_2 \cdot p_{PM}^1(ca_i^{2+}) + a_3 \cdot p_{ER}^{Ca^{2+}} \cdot u_{ER} - a_4 \cdot p_{ER}^1(ca_i^{2+}) \cdot p_{ER}^2(ca_{ER}^{2+})$$

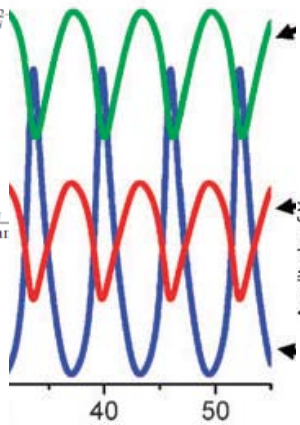
$$\frac{d(ca_{ER}^{2+})}{dt} = \frac{V_i - V_{ER}}{V_{ER}} \cdot (-a_3 \cdot p_{ER}^{Ca^{2+}} \cdot ca_{ER}^{2+} + a_4 \cdot p_{ER}^1(ca_i^{2+}) \cdot p_{ER}^2(ca_{ER}^{2+})),$$

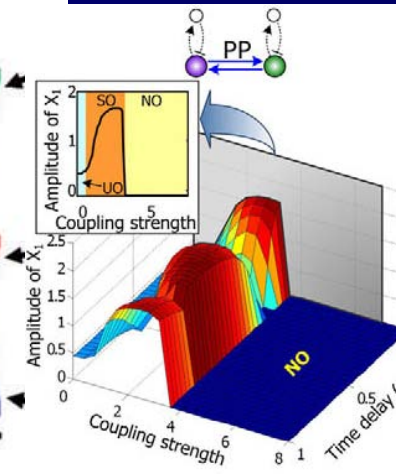
$$\frac{d(ip3)}{dt} = m_0 \cdot \frac{camp_e}{k_G + camp_e} + m_1 \cdot \frac{(ca_i^{2+})^4}{(k_{Ca^{2+}} + ca_i^{2+})^4} + ap - m_2 \cdot \frac{ip3}{k_{ip} + ip3},$$

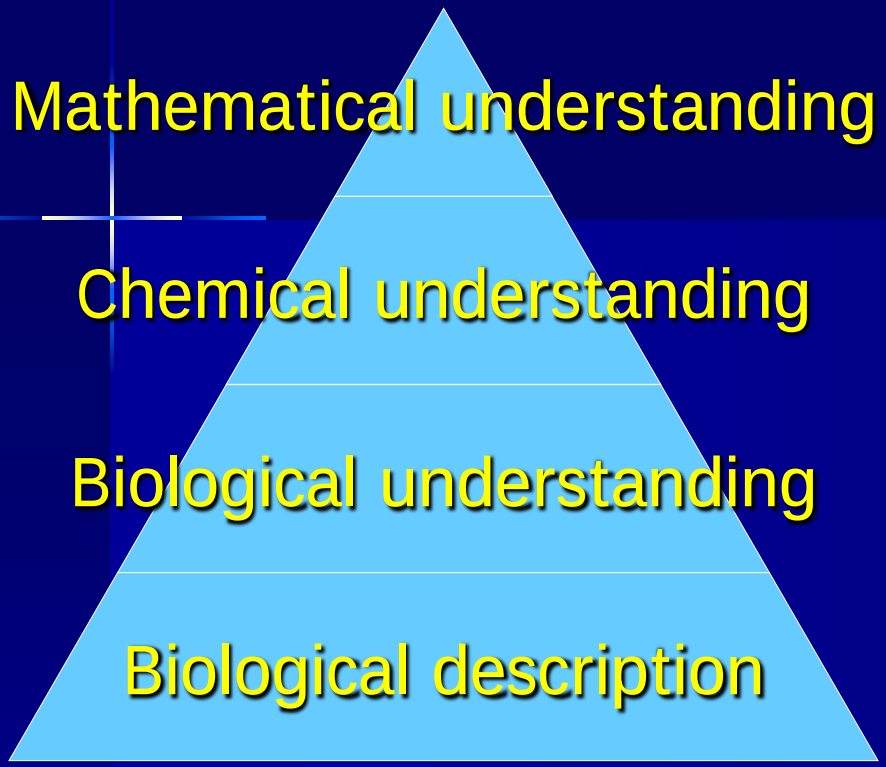
$$\frac{d(camp_i)}{dt} = D_{ACA} \cdot aca^* - j_{cAMPi} - RegA_i \cdot \frac{camp_i}{k_{RegA} + car} \cdot \frac{k_{ER}}{k_{ER} + ca_{ER}^{2+}},$$

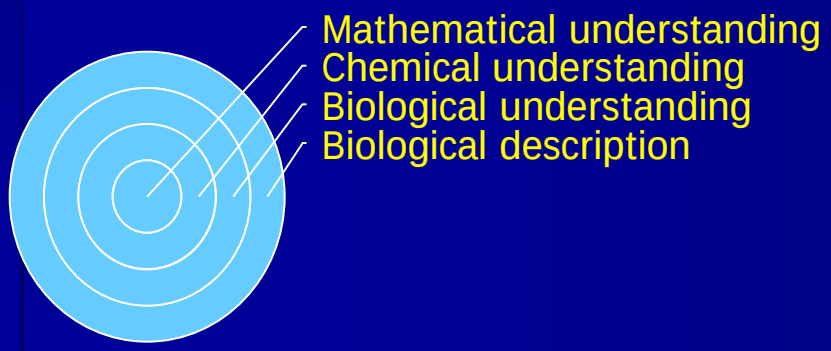
$$\frac{d(camp_e)}{dt} = j_{cAMPi} + j_{cAMPe} - PDE_e \cdot \frac{camp_e}{k_{PDE} + camp_e},$$

$$\frac{d(erk2)}{dt} = d_1 \cdot \left(\frac{pka}{c_1} \cdot (1 - erk2) - erk2\right),$$

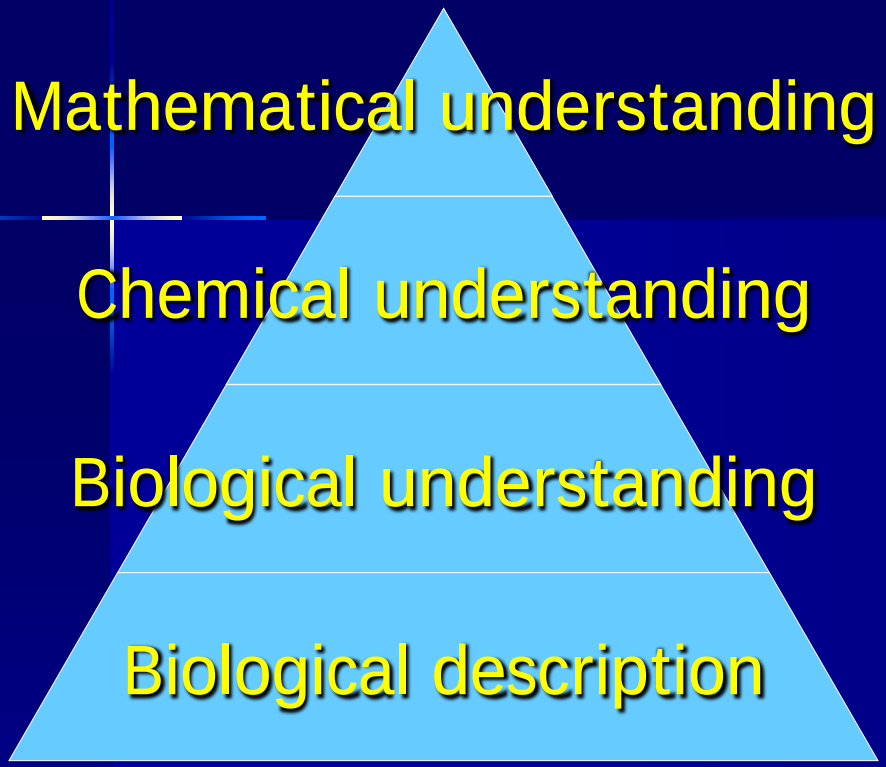




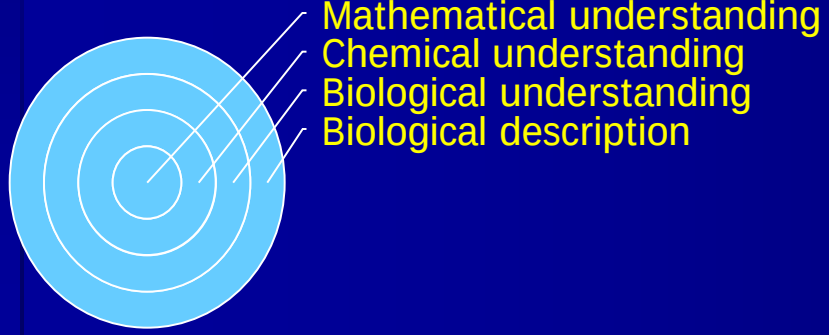

Mathematical understanding
Chemical understanding
Biological understanding
Biological description


Mathematical understanding
Chemical understanding
Biological understanding
Biological description

Public understanding
Political understanding



Public science day in Bristol Aug 2010.



PHH talking to former science minister Lord Paul Drayson 12 Sept 2010 about excellent of British science and need for champions of research

Networks, noise and nodes

- understanding to
- UNDERSTANDING
- consequences to
- CONSEQUENCES

Resources: phh4@le.ac.uk

- www.molcyt.com
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- www.AoBBlog.com

Declan Bates, Kwang-Hyun Cho (and lab), Jongrae Kim, Najl Valeyev, Ian Postlethwaite, Jung-Su Kim