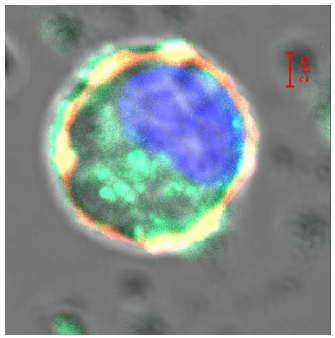
Intra-cellular Control of Insulin Secretion

Application of Control Theory and Optimization Techniques in Biochemical Pathways, ACTOpTBiP

SatMeet-ICM2010, 16-18 August 2010, Hyderabad, India - revised

Bernhelm Booß-Bavnbek, Roskilde University, Denmark
booss@ruc.dk



Outline

Outline

Outline

Outline

Outline

Bio-Math topics: old and new

Traditional objects of mathematical modeling in biology and medicine:

- inherited genotypes (e.g., Hardy-Weinberg equilibrium)
- population dynamics and epidemiology of infectious diseases
- chemotaxis
- physiology of blood circulation and drug uptake

Challenging biochemical pathways:

- impressive recent progress in quality and quantity of available data
- the promises of faster and larger computers
- imbalance between fast growing med care costs (health industrial complex) and virtual stagnation in understanding and treatment/cure

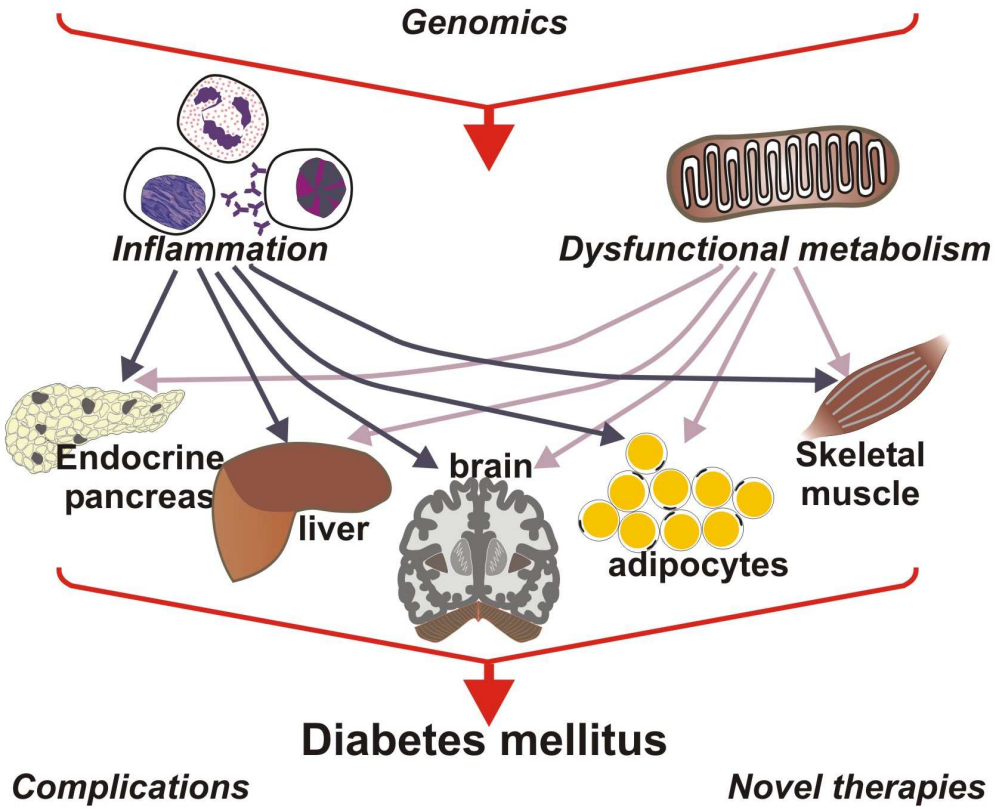
Time to follow d'Alembert's advise?

Jean le Rond d'Alembert's verdict (1752):

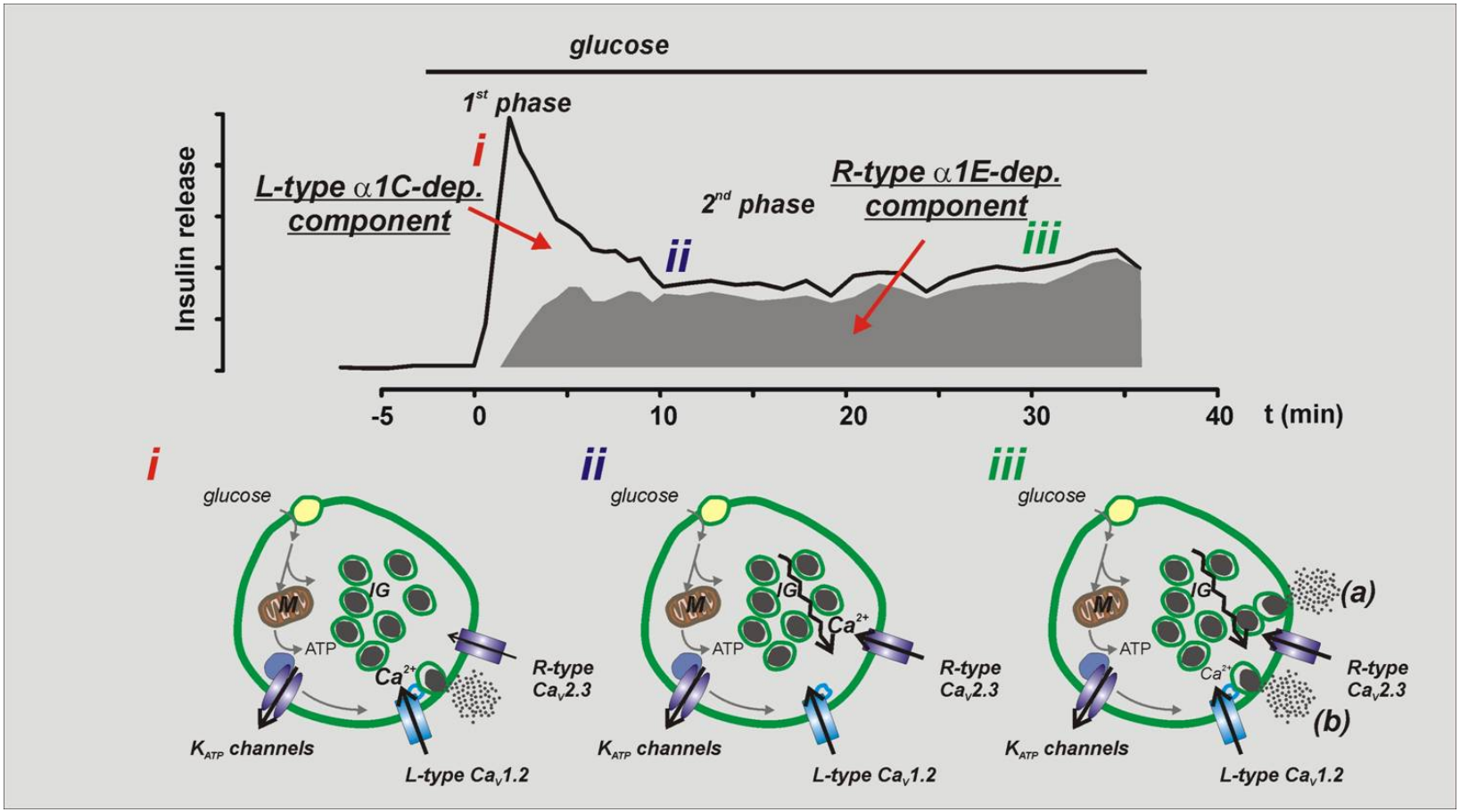
Some have tried to reduce even the art of curing to calculations; and the human body, that most complicated machine, has been treated by our algebraic doctors as if it were the simplest or the easiest one to reduce to its component parts. It is a curious thing to see these authors solve with the stroke of a pen problems of hydraulics and statics capable of occupying the greatest geometers for a whole lifetime.

As for us who are wiser or more timid, let us be content to view most of these calculations and vague suppositions as intellectual games to which Nature is not obliged to conform, and let us conclude that the single true method of philosophizing as physical scientists consists either in the application of mathematical analysis to experiments, or in observation alone, enlightened by the spirit of method, aided sometimes by conjectures when they can furnish some insights, but rigidly dissociated from any arbitrary hypotheses.

Scientific Areas in Diabetes Research



Biphasic insulin secretion in the single pancreatic β-cell, from E. Renström



Medicine challenge I: understand, predict, and cure impaired insulin secretion

Investigations of cell mechanics and cell function
$\rightarrow$ Clinical applications, *theranostics*, and pharma perspective

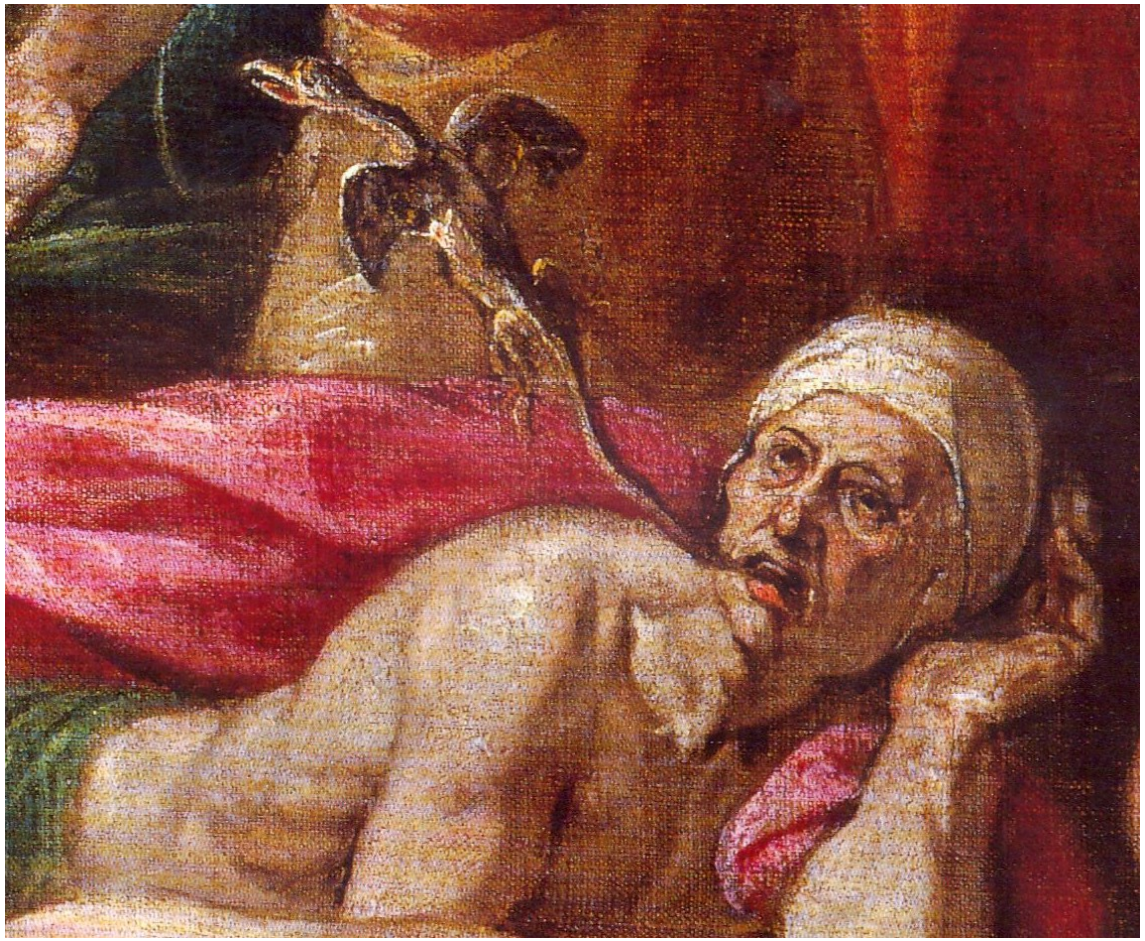
- Untangle the symptomatic definition of *diabetes m.*
- Epigenetic / epigenomic identification of the function, protein overexpression or suppression of critical genes, case India?
- Early and accurate diagnosis by gene sequencing and in-vivo inspection
- Quality control of transplants for T1D
- Precise drug delivery
- β-cell pace maker
- Test of drug components and nanotoxicity

Medicine challenge I: understand, predict, and cure impaired insulin secretion

Investigations of cell mechanics and cell function
$\rightarrow$ Clinical applications, *theranostics*, and pharma perspective

- Untangle the symptomatic definition of *diabetes m.*
- Epigenetic / epigenomic identification of the function, protein overexpression or suppression of critical genes, case India?
- Early and accurate diagnosis by gene sequencing and in-vivo inspection
- Quality control of transplants for T1D
- Precise drug delivery
- β-cell pace maker
- Test of drug components and nanotoxicity

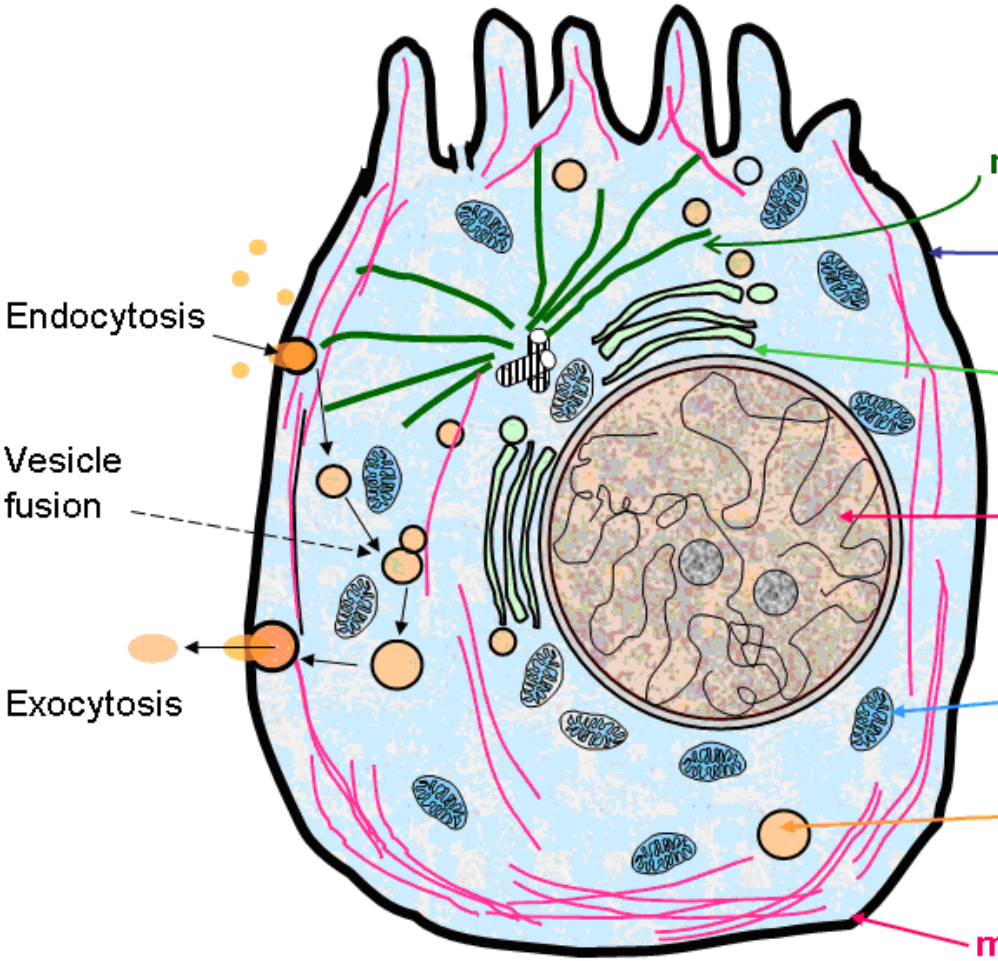
Medicine challenge II: get the information out before putting the drugs in (Crispin van den Broeck, Healing the sick, 1577)



External control requires to

* understand nature's internal control and optimization - here electromagnetism
* build and test a physical model - here dynamic marker of organelles by luminescent magnetic beads

Selected structures and functions of an animal cell I



microtubules: Ø 25 nm; ≤100 µm

surface membrane: 8 nm across
-> boundary inside/outside

endoplasmatic reticulum: width 250 nm
-> protein synthesis and modification

nucleus: Ø 5 µm -> genetic material;
central control of cellular functions

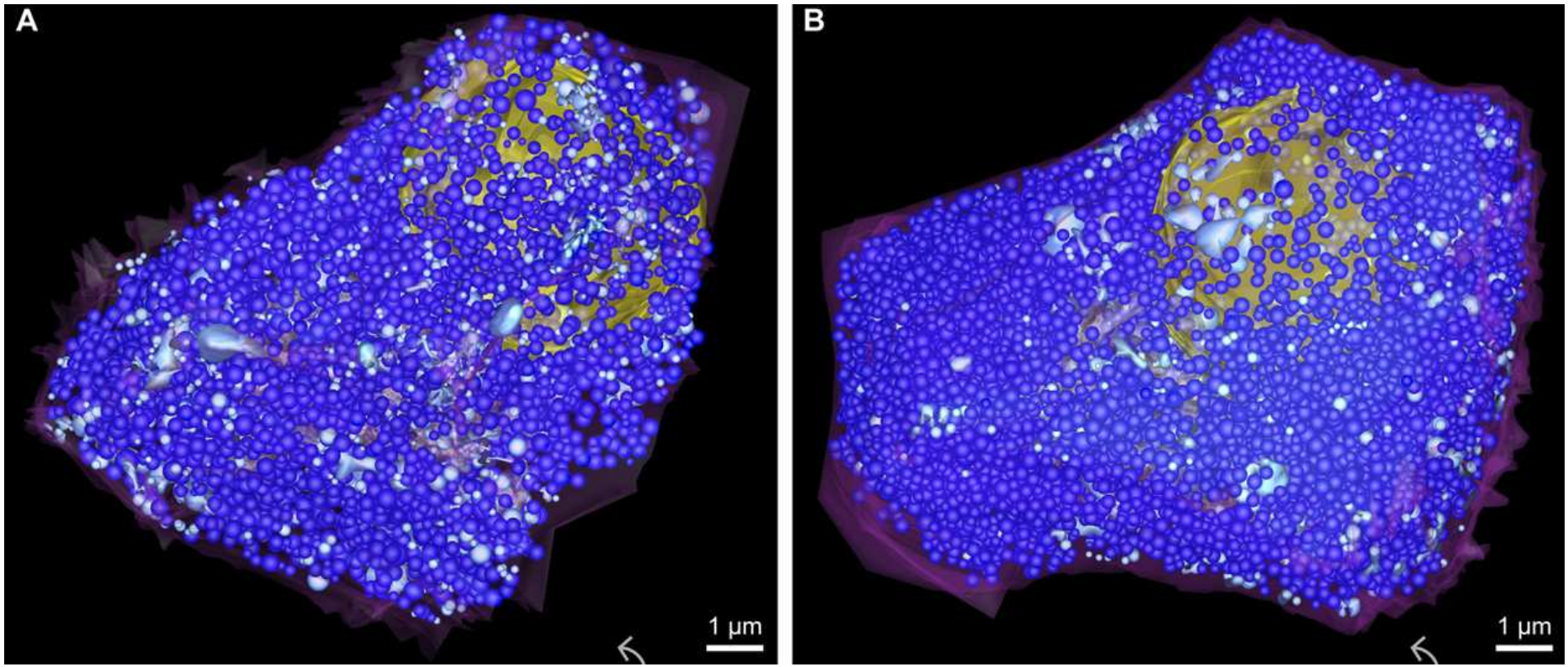
mitochondria: 1 µm -> cellular respiration

vesicles: -> storage of cell products
and export material ; functional centers

microfilaments: Ø 6 nm

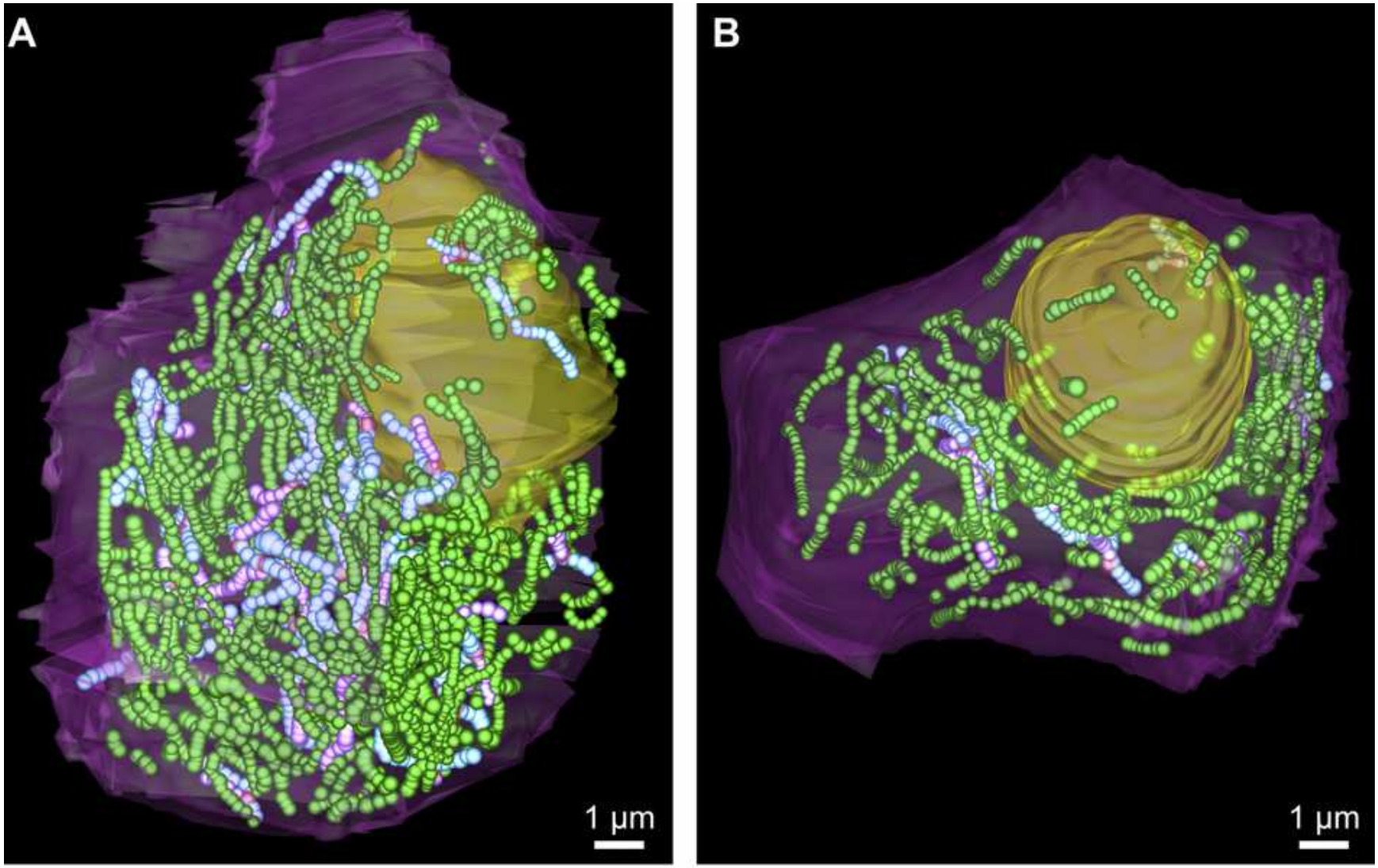
Source: A. Otto, General picture of secretory cells

Selected structures and functions of an animal cell II



Electron tomograph of two β-cells with blue marked insulin granules and yellow marked nucleus. Left after release, right not releasing.
Source: B. Marsh and collaborators, 2007

Selected structures and functions of an animal cell III

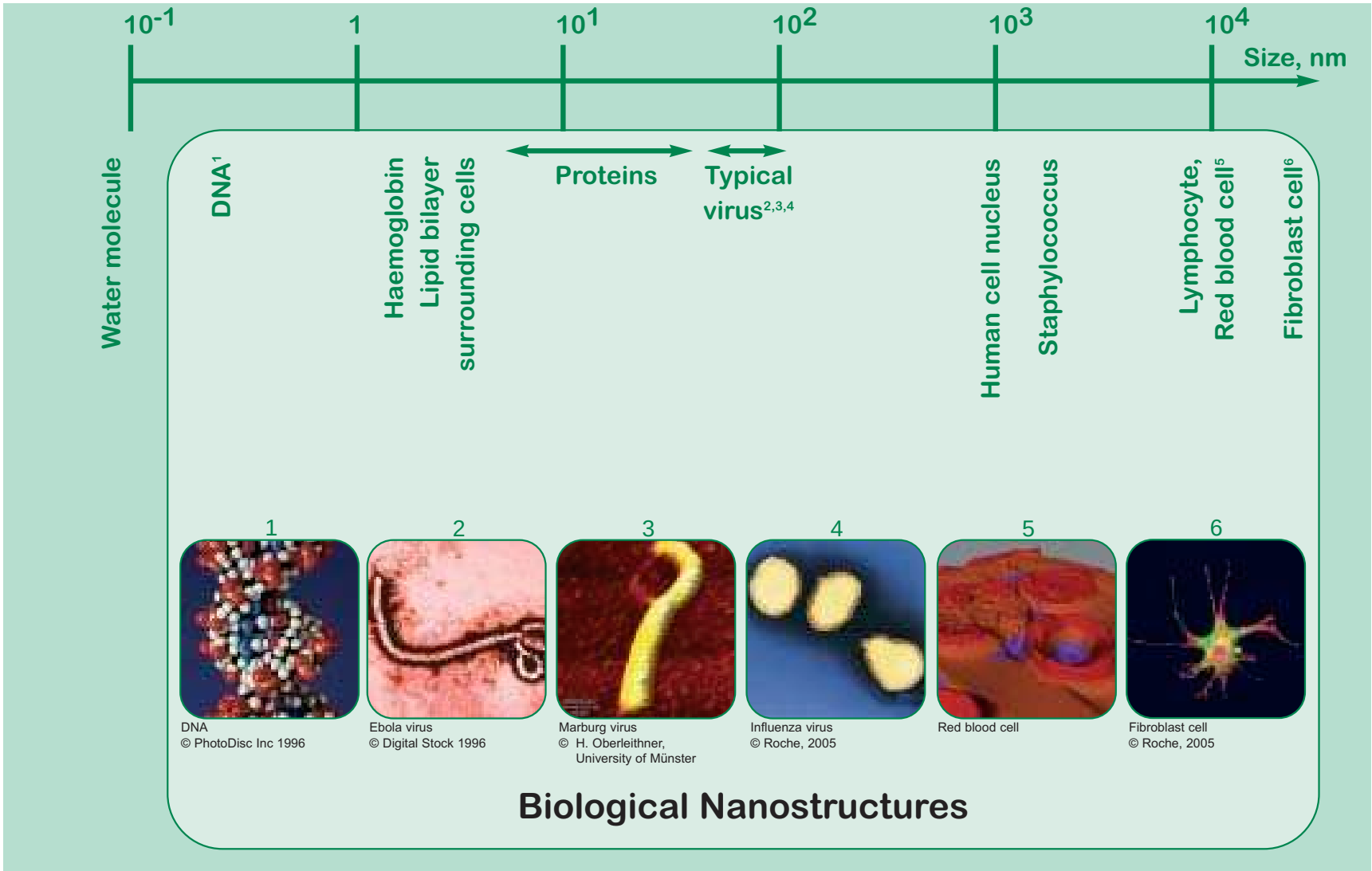


Green marked, partly branched mitochondria; branch points in red

Biology problems: vesicular traffic

1. Intracellular (cytosol) viscosity
   - Near plasma membrane vs. bulk
   - Before release vs. after
   - Healthy cells vs. stressed (or genetic deviating)
2. Metabolism, mitochondria shape, Ca^{++} oscillations
3. Actin pathways
4. 2-phase secretion
5. Flickering of fusion event
6. Gene function and gene silencing by short interfering RNA
7. Abundance of new phenomena
   - Multi-scale in time and length
   - Multi-level from DNA to secretion
   - Presence of relicts (possibly meaningless phylogenetic ruins)

Typical nano sizes, from European technology platform on nanomedicine, Brussels 2005



Capturing granule dynamics by nanotechnology

Goals:

1. Labelling and imaging pancreatic β-cell proteins
2. Characterization of the β-cell cytoplasm
3. Tracking the 2-phase secretion and the flickering

Deplorable state-of-the-art:

MRI Powerful imaging time sequences of living β-cell islets

- poor resolution, blind for intracellular states and processes
- not applicable to early diagnosis of β-cell mass or functional status

ET Powerful high spatial resolution of organelles and other relevant intracellular states in fixed cells

- unable to fast acquisition of events in living cells

Clamp Powerful membrane electro-physiology, potential measuring, blind for intra-cellular dynamics

$\longrightarrow$ Fill precision gap between position and dynamics

- intelligent model based use of new-type nanoparticles.

Capturing granule dynamics by nanotechnology

Goals:

1. Labelling and imaging pancreatic β-cell proteins
2. Characterization of the β-cell cytoplasm
3. Tracking the 2-phase secretion and the flickering

Deplorable state-of-the-art:

MRI Powerful imaging time sequences of living β-cell islets
- poor resolution, blind for intracellular states and processes
- not applicable to early diagnosis of β-cell mass or functional status

ET Powerful high spatial resolution of organelles and other relevant intracellular states in fixed cells
- unable to fast acquisition of events in living cells

Clamp Powerful membrane electro-physiology, potential measuring, blind for intra-cellular dynamics

$\longrightarrow$ Fill precision gap between position and dynamics
- intelligent model based use of new-type nanoparticles.

Nanotechnology “deliverables"

- Separation of excitation and light emission (after-glows) to reduce background radiation
- Prolonged luminescence
- Magneto-luminescent particles
- Antibody preparation
- Biocompatibility, nanotoxicity
- Controlled movement by electro-dynamic field generator
  - Gentle transport across plasma membrane
  - Controlled intra-cellular pull and turn
- Light microscopy $\longrightarrow$ Nanoscopy hierarchy *in vivo*
  - Cell lines, primary cells of model animals, human cells, organs, animals and patients
  - Accessible secretory cells (e.g., chromaffin cells) $\rightarrow$ delicate secretory cells (β-cells and nerve cells)

Nanotechnology “deliverables"

- Separation of excitation and light emission (after-glows) to reduce background radiation
- Prolonged luminescence
- Magneto-luminescent particles
- Antibody preparation
- Biocompatibility, nanotoxicity
- Controlled movement by electro-dynamic field generator
  - Gentle transport across plasma membrane
  - Controlled intra-cellular pull and turn
- Light microscopy $\longrightarrow$ Nanoscopy hierarchy *in vivo*
  - Cell lines, primary cells of model animals, human cells, organs, animals and patients
  - Accessible secretory cells (e.g., chromaffin cells) $\rightarrow$ delicate secretory cells (β-cells and nerve cells)

Nanotechnology “deliverables"

- Separation of excitation and light emission (after-glows) to reduce background radiation
- Prolonged luminescence
- Magneto-luminescent particles
- Antibody preparation
- Biocompatibility, nanotoxicity
- Controlled movement by electro-dynamic field generator
  - Gentle transport across plasma membrane
  - Controlled intra-cellular pull and turn
- Light microscopy $\longrightarrow$ Nanoscopy hierarchy *in vivo*
  - Cell lines, primary cells of model animals, human cells, organs, animals and patients
  - Accessible secretory cells (e.g., chromaffin cells) $\rightarrow$ delicate secretory cells (β-cells and nerve cells)

Nanotechnology “deliverables"

- Separation of excitation and light emission (after-glows) to reduce background radiation
- Prolonged luminescence
- Magneto-luminescent particles
- Antibody preparation
- Biocompatibility, nanotoxicity
- Controlled movement by electro-dynamic field generator
  - Gentle transport across plasma membrane
  - Controlled intra-cellular pull and turn
- Light microscopy $\longrightarrow$ Nanoscopy hierarchy *in vivo*
  - Cell lines, primary cells of model animals, human cells, organs, animals and patients
  - Accessible secretory cells (e.g., chromaffin cells) $\rightarrow$ delicate secretory cells (β-cells and nerve cells)

Nanotechnology “deliverables"

- Separation of excitation and light emission (after-glows) to reduce background radiation
- Prolonged luminescence
- Magneto-luminescent particles
- Antibody preparation
- Biocompatibility, nanotoxicity
- Controlled movement by electro-dynamic field generator
  - Gentle transport across plasma membrane
  - Controlled intra-cellular pull and turn
- Light microscopy $\longrightarrow$ Nanoscopy hierarchy *in vivo*
  - Cell lines, primary cells of model animals, human cells, organs, animals and patients
  - Accessible secretory cells (e.g., chromaffin cells) $\rightarrow$ delicate secretory cells (β-cells and nerve cells)

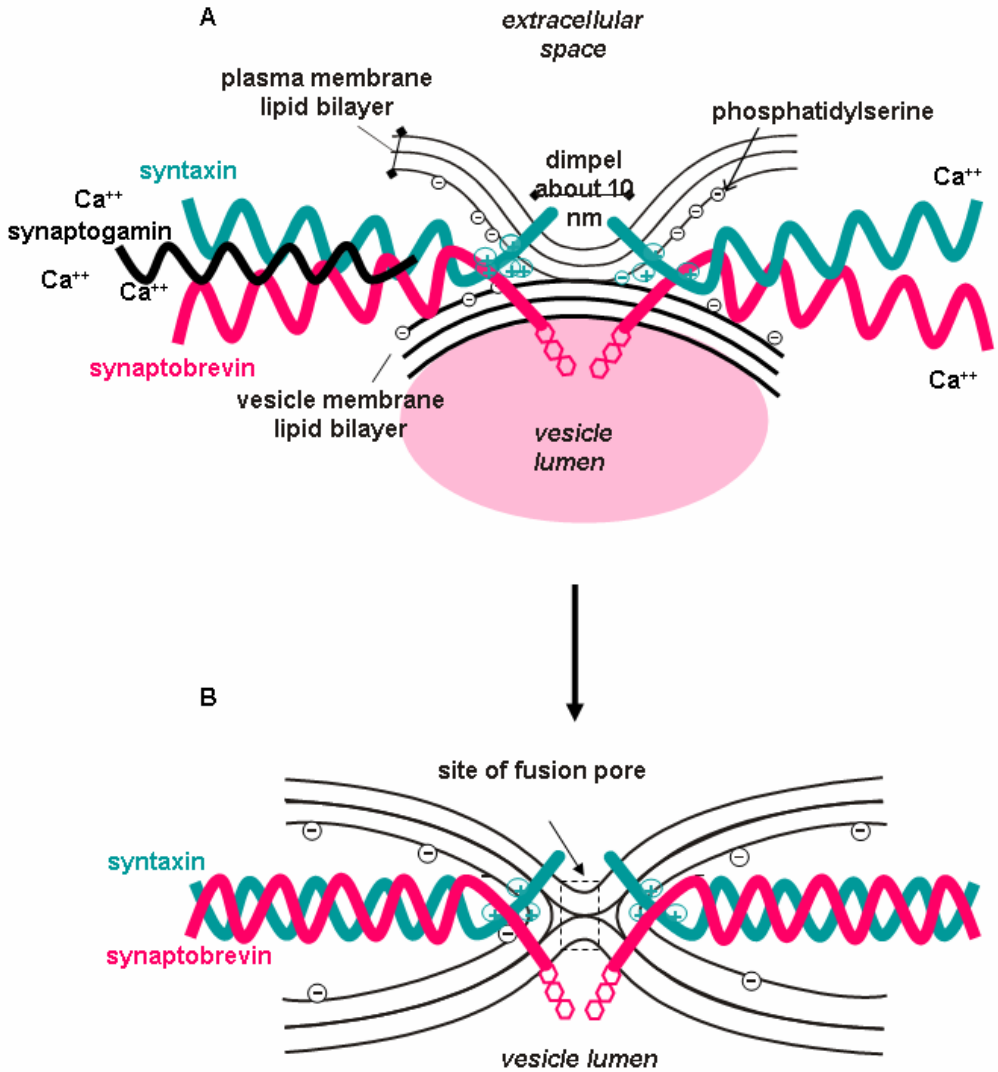
Nanotechnology “deliverables"

- Separation of excitation and light emission (after-glows) to reduce background radiation
- Prolonged luminescence
- Magneto-luminescent particles
- Antibody preparation
- Biocompatibility, nanotoxicity
- Controlled movement by electro-dynamic field generator
  - Gentle transport across plasma membrane
  - Controlled intra-cellular pull and turn
- Light microscopy $\longrightarrow$ Nanoscopy hierarchy *in vivo*
  - Cell lines, primary cells of model animals, human cells, organs, animals and patients
  - Accessible secretory cells (e.g., chromaffin cells) $\rightarrow$ delicate secretory cells (β-cells and nerve cells)

Nanotechnology “deliverables"

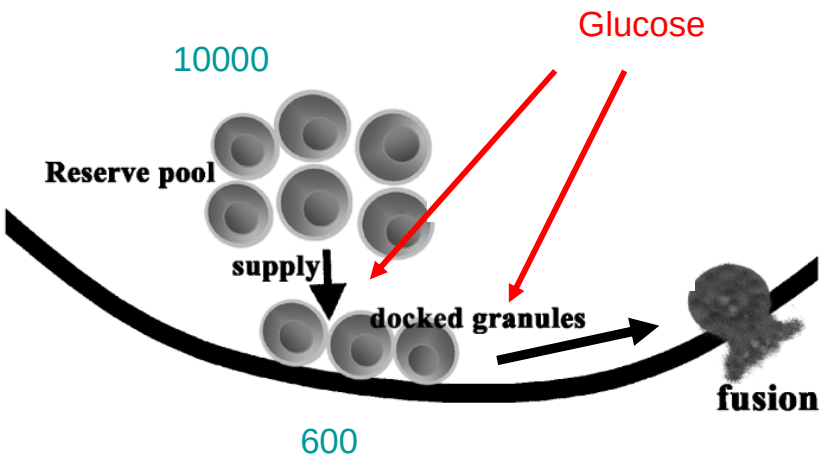
- Separation of excitation and light emission (after-glows) to reduce background radiation
- Prolonged luminescence
- Magneto-luminescent particles
- Antibody preparation
- Biocompatibility, nanotoxicity
- Controlled movement by electro-dynamic field generator
  - Gentle transport across plasma membrane
  - Controlled intra-cellular pull and turn
- Light microscopy $\longrightarrow$ Nanoscopy hierarchy *in vivo*
  - Cell lines, primary cells of model animals, human cells, organs, animals and patients
  - Accessible secretory cells (e.g., chromaffin cells) $\rightarrow$ delicate secretory cells (β-cells and nerve cells)

Bilayer membrane fusion



Basic Two-Pool Model for Exocytosis

G.M. Grodsky, 1972

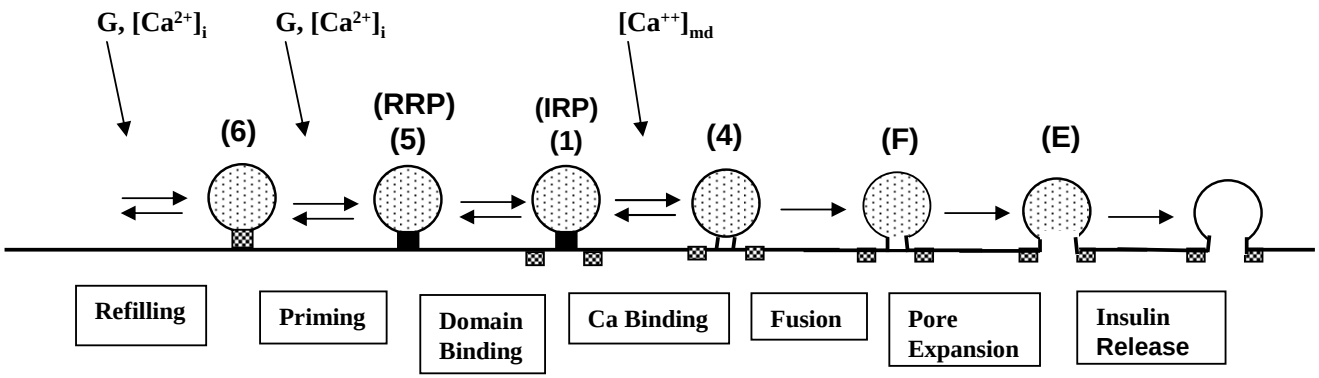


- First phase due to release of labile pool
- Second phase due to re-supply of labile pool

Conventional compartment modelling II

Chen-Wang-Sherman Model

200 25 15



BJ 95:2226-41 2008

Ca^{++} Oscillations, directed in space and time

$\mathcal{D}$ Alternating electrical field density of low frequency

$$f = \begin{cases} \sim 5\,\mathrm{Hz} & \text{for } \beta \text{ cells} \\ \sim 100\,\mathrm{Hz} & \text{for nerve cells} \end{cases}$$

$\mathcal{E}$ Corresponding electrical field

$\mathcal{H}$ Resulting magnetic field wave

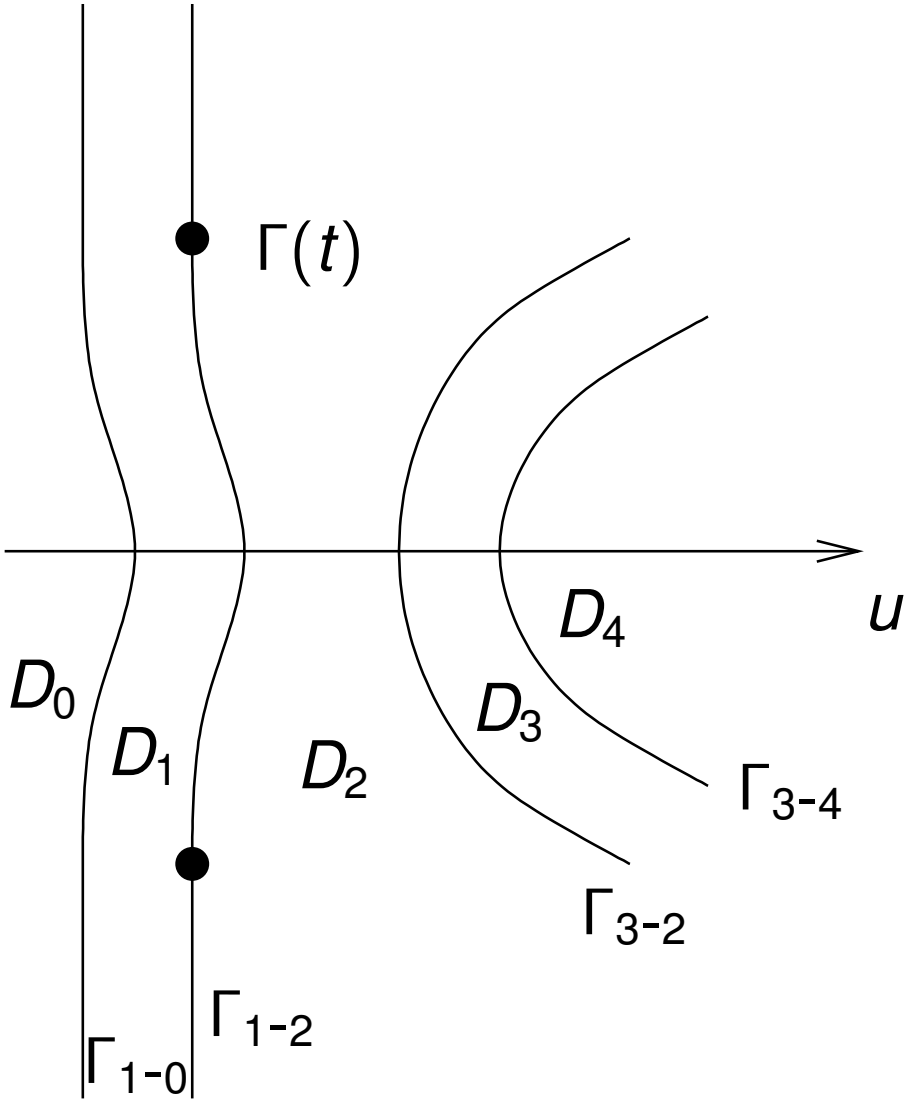
$\mathcal{B}$ Corresponding magnetic flux density $\mathcal{B} = \mu\mathcal{H}$, permeability $\mu = \mu_0\mu_r$, field amplitude $\widehat{\mathcal{B}}$

X_C Capacitive reactance $X_C := 1/(\omega C)$

- $\omega = 2\pi f$, C capacitance
- Recall $Z = R - iX_C$ complex impedance
- Vanishing on amorphous outside cell neighbourhood and on cytosol
- Forming the dimple implies decreasing X_C until X_C vanishes in the fusion pore

Clearly separated regions

- D_0 Amorphous outside
- D_1 Plasma membrane
- D_2 Cytosol
- D_3 Vesicle membrane
- D_4 Vesicle lumen
  - $\Gamma(t)$ Free boundary
  - u displacement
- $(\{M_j\})$ *Ca* storage organelles: endoplasmic reticulum (ER) and mitochondria, to be activated
- (N) Cell nucleus



Application of control theory to insulin secretion process

Explanation Dimple making

- Hemifusion, fusion pore, flickering
- Apply (electro-magnetic) fundamental equations

Description Check parameters (influences, char. values)

- Energy needed for exocytosis / fusion event
- Field amplitude $\widehat{B}$, frequency f
- Velocity v of field wave and char. time for event
- Number of involved Ca^{++} depots
- Number of Fe^{++} atoms and ferrous compounds in mitochondrial cytochrome enzyme

Prediction Typical and atypical developments

- Explain deficiencies (stress, aging)
- Early diagnosis of type 2 diabetes
- Identify rôle of critical genes and proteins

Prescription Exocytosis pacemaker for type 2 diabetes ?

Application of control theory to insulin secretion process

Explanation Dimple making

- Hemifusion, fusion pore, flickering
- Apply (electro-magnetic) fundamental equations

Description Check parameters (influences, char. values)

- Energy needed for exocytosis / fusion event
- Field amplitude $\widehat{B}$, frequency f
- Velocity v of field wave and char. time for event
- Number of involved Ca^{++} depots
- Number of Fe^{++} atoms and ferrous compounds in mitochondrial cytochrome enzyme

Prediction Typical and atypical developments

- Explain deficiencies (stress, aging)
- Early diagnosis of type 2 diabetes
- Identify rôle of critical genes and proteins

Prescription Exocytosis pacemaker for type 2 diabetes ?

Application of control theory to insulin secretion process

Explanation Dimple making

- Hemifusion, fusion pore, flickering
- Apply (electro-magnetic) fundamental equations

Description Check parameters (influences, char. values)

- Energy needed for exocytosis / fusion event
- Field amplitude $\widehat{\mathcal{B}}$, frequency f
- Velocity v of field wave and char. time for event
- Number of involved Ca^{++} depots
- Number of Fe^{++} atoms and ferrous compounds in mitochondrial cytochrome enzyme

Prediction Typical and atypical developments

- Explain deficiencies (stress, aging)
- Early diagnosis of type 2 diabetes
- Identify rôle of critical genes and proteins

Prescription Exocytosis pacemaker for type 2 diabetes ?

Application of control theory to insulin secretion process

Explanation Dimple making

- Hemifusion, fusion pore, flickering
- Apply (electro-magnetic) fundamental equations

Description Check parameters (influences, char. values)

- Energy needed for exocytosis / fusion event
- Field amplitude $\widehat{\mathcal{B}}$, frequency f
- Velocity v of field wave and char. time for event
- Number of involved Ca^{++} depots
- Number of Fe^{++} atoms and ferrous compounds in mitochondrial cytochrome enzyme

Prediction Typical and atypical developments

- Explain deficiencies (stress, aging)
- Early diagnosis of type 2 diabetes
- Identify rôle of critical genes and proteins

Prescription Exocytosis pacemaker for type 2 diabetes ?

Application of control theory to insulin secretion process

Explanation Dimple making

- Hemifusion, fusion pore, flickering
- Apply (electro-magnetic) fundamental equations

Description Check parameters (influences, char. values)

- Energy needed for exocytosis / fusion event
- Field amplitude $\widehat{\mathcal{B}}$, frequency f
- Velocity v of field wave and char. time for event
- Number of involved Ca^{++} depots
- Number of Fe^{++} atoms and ferrous compounds in mitochondrial cytochrome enzyme

Prediction Typical and atypical developments

- Explain deficiencies (stress, aging)
- Early diagnosis of type 2 diabetes
- Identify rôle of critical genes and proteins

Prescription Exocytosis pacemaker for type 2 diabetes ?

Application of control theory to insulin secretion process

Explanation Dimple making

- Hemifusion, fusion pore, flickering
- Apply (electro-magnetic) fundamental equations

Description Check parameters (influences, char. values)

- Energy needed for exocytosis / fusion event
- Field amplitude $\widehat{\mathcal{B}}$, frequency f
- Velocity v of field wave and char. time for event
- Number of involved Ca^{++} depots
- Number of Fe^{++} atoms and ferrous compounds in mitochondrial cytochrome enzyme

Prediction Typical and atypical developments

- Explain deficiencies (stress, aging)
- Early diagnosis of type 2 diabetes
- Identify rôle of critical genes and proteins

Prescription Exocytosis pacemaker for type 2 diabetes ?

Hypothetical feedback mechanism

1. Build-up of linear array of molecularly bound Ca storages
2. Through chosen vesicle, selecting the hemifusion area on plasma membrane
3. Superposition of locally distributed self-coordinated and self-oriented Ca^{++} activity
4. Generation of a dynamic magnetic field wave $\mathcal{B}$ of low frequency
5. To begin with, high X_C in plasma membrane PM and low $\widehat{\mathcal{B}}$
6. Transmembrane proteins become activated
7. Form change decreases X_C close to the emerging dimple
8. Magnetic field wave enters the plasma membrane more easily
9. Increased current density (sharper bundling)
10. Increased Lorentz force balancing elastic forces
11. Hemifusion, branch point, short circuit, fusion pore

Hypothetical feedback mechanism

1. Build-up of linear array of molecularly bound *Ca* storages
2. Through chosen vesicle, selecting the hemifusion area on plasma membrane
3. Superposition of locally distributed self-coordinated and self-oriented Ca^{++} activity
4. Generation of a dynamic magnetic field wave $\mathcal{B}$ of low frequency
5. To begin with, high X_C in plasma membrane *PM* and low $\widehat{\mathcal{B}}$
6. Transmembrane proteins become activated
7. Form change decreases X_C close to the emerging dimple
8. Magnetic field wave enters the plasma membrane more easily
9. Increased current density (sharper bundling)
10. Increased Lorentz force balancing elastic forces
11. Hemifusion, branch point, short circuit, fusion pore

Hypothetical feedback mechanism

1. Build-up of linear array of molecularly bound *Ca* storages
2. Through chosen vesicle, selecting the hemifusion area on plasma membrane
3. Superposition of locally distributed self-coordinated and self-oriented Ca^{++} activity
4. Generation of a dynamic magnetic field wave $\mathcal{B}$ of low frequency
5. To begin with, high X_C in plasma membrane *PM* and low $\widehat{\mathcal{B}}$
6. Transmembrane proteins become activated
7. Form change decreases X_C close to the emerging dimple
8. Magnetic field wave enters the plasma membrane more easily
9. Increased current density (sharper bundling)
10. Increased Lorentz force balancing elastic forces
11. Hemifusion, branch point, short circuit, fusion pore

Hypothetical feedback mechanism

1. Build-up of linear array of molecularly bound *Ca* storages
2. Through chosen vesicle, selecting the hemifusion area on plasma membrane
3. Superposition of locally distributed self-coordinated and self-oriented Ca^{++} activity
4. Generation of a dynamic magnetic field wave $\mathcal{B}$ of low frequency
5. To begin with, high X_C in plasma membrane *PM* and low $\widehat{\mathcal{B}}$
6. Transmembrane proteins become activated
7. Form change decreases X_C close to the emerging dimple
8. Magnetic field wave enters the plasma membrane more easily
9. Increased current density (sharper bundling)
10. Increased Lorentz force balancing elastic forces
11. Hemifusion, branch point, short circuit, fusion pore

Hypothetical feedback mechanism

1. Build-up of linear array of molecularly bound *Ca* storages
2. Through chosen vesicle, selecting the hemifusion area on plasma membrane
3. Superposition of locally distributed self-coordinated and self-oriented Ca^{++} activity
4. Generation of a dynamic magnetic field wave $\mathcal{B}$ of low frequency
5. To begin with, high X_C in plasma membrane *PM* and low $\widehat{\mathcal{B}}$
6. Transmembrane proteins become activated
7. Form change decreases X_C close to the emerging dimple
8. Magnetic field wave enters the plasma membrane more easily
9. Increased current density (sharper bundling)
10. Increased Lorentz force balancing elastic forces
11. Hemifusion, branch point, short circuit, fusion pore

Hypothetical feedback mechanism

1. Build-up of linear array of molecularly bound *Ca* storages
2. Through chosen vesicle, selecting the hemifusion area on plasma membrane
3. Superposition of locally distributed self-coordinated and self-oriented Ca^{++} activity
4. Generation of a dynamic magnetic field wave $\mathcal{B}$ of low frequency
5. To begin with, high X_C in plasma membrane *PM* and low $\widehat{\mathcal{B}}$
6. Transmembrane proteins become activated
7. Form change decreases X_C close to the emerging dimple
8. Magnetic field wave enters the plasma membrane more easily
9. Increased current density (sharper bundling)
10. Increased Lorentz force balancing elastic forces
11. Hemifusion, branch point, short circuit, fusion pore

Hypothetical feedback mechanism

1. Build-up of linear array of molecularly bound *Ca* storages
2. Through chosen vesicle, selecting the hemifusion area on plasma membrane
3. Superposition of locally distributed self-coordinated and self-oriented Ca^{++} activity
4. Generation of a dynamic magnetic field wave $\mathcal{B}$ of low frequency
5. To begin with, high X_C in plasma membrane *PM* and low $\widehat{\mathcal{B}}$
6. Transmembrane proteins become activated
7. Form change decreases X_C close to the emerging dimple
8. Magnetic field wave enters the plasma membrane more easily
9. Increased current density (sharper bundling)
10. Increased Lorentz force balancing elastic forces
11. Hemifusion, branch point, short circuit, fusion pore

Hypothetical feedback mechanism

1. Build-up of linear array of molecularly bound *Ca* storages
2. Through chosen vesicle, selecting the hemifusion area on plasma membrane
3. Superposition of locally distributed self-coordinated and self-oriented Ca^{++} activity
4. Generation of a dynamic magnetic field wave $\mathcal{B}$ of low frequency
5. To begin with, high X_C in plasma membrane *PM* and low $\widehat{\mathcal{B}}$
6. Transmembrane proteins become activated
7. Form change decreases X_C close to the emerging dimple
8. Magnetic field wave enters the plasma membrane more easily
9. Increased current density (sharper bundling)
10. Increased Lorentz force balancing elastic forces
11. Hemifusion, branch point, short circuit, fusion pore

Hypothetical feedback mechanism

1. Build-up of linear array of molecularly bound Ca storages
2. Through chosen vesicle, selecting the hemifusion area on plasma membrane
3. Superposition of locally distributed self-coordinated and self-oriented Ca^{++} activity
4. Generation of a dynamic magnetic field wave $\mathcal{B}$ of low frequency
5. To begin with, high X_C in plasma membrane PM and low $\widehat{\mathcal{B}}$
6. Transmembrane proteins become activated
7. Form change decreases X_C close to the emerging dimple
8. Magnetic field wave enters the plasma membrane more easily
9. Increased current density (sharper bundling)
10. Increased Lorentz force balancing elastic forces
11. Hemifusion, branch point, short circuit, fusion pore

Hypothetical feedback mechanism

1. Build-up of linear array of molecularly bound Ca storages
2. Through chosen vesicle, selecting the hemifusion area on plasma membrane
3. Superposition of locally distributed self-coordinated and self-oriented Ca^{++} activity
4. Generation of a dynamic magnetic field wave $\mathcal{B}$ of low frequency
5. To begin with, high X_C in plasma membrane PM and low $\widehat{\mathcal{B}}$
6. Transmembrane proteins become activated
7. Form change decreases X_C close to the emerging dimple
8. Magnetic field wave enters the plasma membrane more easily
9. Increased current density (sharper bundling)
10. Increased Lorentz force balancing elastic forces
11. Hemifusion, branch point, short circuit, fusion pore

Hypothetical feedback mechanism

1. Build-up of linear array of molecularly bound Ca storages
2. Through chosen vesicle, selecting the hemifusion area on plasma membrane
3. Superposition of locally distributed self-coordinated and self-oriented Ca^{++} activity
4. Generation of a dynamic magnetic field wave $\mathcal{B}$ of low frequency
5. To begin with, high X_C in plasma membrane PM and low $\widehat{\mathcal{B}}$
6. Transmembrane proteins become activated
7. Form change decreases X_C close to the emerging dimple
8. Magnetic field wave enters the plasma membrane more easily
9. Increased current density (sharper bundling)
10. Increased Lorentz force balancing elastic forces
11. Hemifusion, branch point, short circuit, fusion pore

The free boundary problem, simplified

$u(x, y, z, t)$ membrane displacement from equilibrium

$\Gamma = \{\Gamma(t), t\} =$ boundary of {u=0} free boundary

Forces $m\frac{\partial^2 u}{\partial t^2} = \mathcal{F}_L + \mathcal{F}_T + \mathcal{F}_M$

- $\mathcal{F}_L = q\mathcal{E}_{\text{space}} + q(\mathfrak{v} \times \mathcal{B}) - \gamma\mathfrak{v}_1$ Lorentz force
- $\mathcal{F}_T$ Transmembrane proteins' force
- $\mathcal{F}_M = \frac{T_0}{\rho}\left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2}\right) - \frac{2}{T_1}\frac{\partial u}{\partial t}$ Visco-elastic force, ρ density, T_0 tension, T_1 relaxation time
- $\frac{\partial^2 u}{\partial t^2} \ll 1$ quasi-static process
- $\frac{\partial u}{\partial t} > 0$ not assumed, i.e., flickering admitted

Normalized equation $\Delta u - \frac{\partial u}{\partial t} = f$ on $u > 0$, f force density $\Longrightarrow$ qualitative results on regularity of process by free boundary value theory

The free boundary problem, simplified

$u(x, y, z, t)$ membrane displacement from equilibrium

$\Gamma = \{\Gamma(t), t\} =$ boundary of {u=0} free boundary

Forces $m\frac{\partial^2 u}{\partial t^2} = \mathcal{F}_L + \mathcal{F}_T + \mathcal{F}_M$

- $\mathcal{F}_L = q\mathcal{E}_{\text{space}} + q\big(\mathfrak{v} \times \mathcal{B}\big) - \gamma\mathfrak{v}_1$ Lorentz force
- $\mathcal{F}_T$ Transmembrane proteins' force
- $\mathcal{F}_M = \frac{T_0}{\rho}\left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2}\right) - \frac{2}{T_1}\frac{\partial u}{\partial t}$ Visco-elastic force, ρ density, T_0 tension, T_1 relaxation time
- $\frac{\partial^2 u}{\partial t^2} \ll 1$ quasi-static process
- $\frac{\partial u}{\partial t} > 0$ not assumed, i.e., flickering admitted

Normalized equation $\Delta u - \frac{\partial u}{\partial t} = f$ on $u > 0$, f force density $\Longrightarrow$ qualitative results on regularity of process by free boundary value theory

The free boundary problem, simplified

$u(x, y, z, t)$ membrane displacement from equilibrium

$\Gamma = \{\Gamma(t), t\} =$ boundary of {u=0} free boundary

Forces $m\frac{\partial^2 u}{\partial t^2} = \mathcal{F}_L + \mathcal{F}_T + \mathcal{F}_M$

- $\mathcal{F}_L = q\mathcal{E}_{\text{space}} + q\big(\mathfrak{v} \times \mathcal{B}\big) - \gamma\mathfrak{v}_1$ Lorentz force
- $\mathcal{F}_T$ Transmembrane proteins' force
- $\mathcal{F}_M = \frac{T_0}{\rho}\left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2}\right) - \frac{2}{T_1}\frac{\partial u}{\partial t}$ Visco-elastic force, ρ density, T_0 tension, T_1 relaxation time
- $\frac{\partial^2 u}{\partial t^2} \ll 1$ quasi-static process
- $\frac{\partial u}{\partial t} > 0$ not assumed, i.e., flickering admitted

Normalized equation $\Delta u - \frac{\partial u}{\partial t} = f$ on $u > 0$, f force density $\Longrightarrow$ qualitative results on regularity of process by free boundary value theory

Modelling biochemical pathways requires paradigm shift

1. Repair medicine $\rightarrow$ Traditional health investigation
2. Drawing and labelling magnified pictures
   $\rightarrow$ Investigation of theoretically defined magnitudes
3. Holism (*Systems biology*)
   Reductionism (e.g., material properties of *model membranes*)
   $\rightarrow$ Confinement of single events
4. Ad-hoc fancied mechanisms (predominance of the visible, contempt of the invisible)
   $\rightarrow$ Fundamental laws (*The visible must be explained in terms of the invisible*, Y. Manin)
5. Systems of ordinary differential equations
   $\rightarrow$ Global analysis, pde, geometry
6. “Modelling" and “simulation"
   $\rightarrow$ Mathematization and physical modelling

Modelling biochemical pathways requires paradigm shift

1. Repair medicine $\rightarrow$ Traditional health investigation
2. Drawing and labelling magnified pictures
   $\rightarrow$ Investigation of theoretically defined magnitudes
3. Holism (*Systems biology*)
   Reductionism (e.g., material properties of *model membranes*)
   $\rightarrow$ Confinement of single events
4. Ad-hoc fancied mechanisms (predominance of the visible, contempt of the invisible)
   $\rightarrow$ Fundamental laws (*The visible must be explained in terms of the invisible*, Y. Manin)
5. Systems of ordinary differential equations
   $\rightarrow$ Global analysis, pde, geometry
6. “Modelling" and “simulation"
   $\rightarrow$ Mathematization and physical modelling

Modelling biochemical pathways requires paradigm shift

1. Repair medicine $\rightarrow$ Traditional health investigation
2. Drawing and labelling magnified pictures
   $\rightarrow$ Investigation of theoretically defined magnitudes
3. $\left\{\begin{array}{l}\text{Holism (}\textit{Systems biology}\text{)}\\ \text{Reductionism (e.g., material properties of }\textit{model membranes}\text{)}\end{array}\right.$
   $\rightarrow$ Confinement of single events
4. Ad-hoc fancied mechanisms (predominance of the visible, contempt of the invisible)
   $\rightarrow$ Fundamental laws (*The visible must be explained in terms of the invisible*, Y. Manin)
5. Systems of ordinary differential equations
   $\rightarrow$ Global analysis, pde, geometry
6. “Modelling" and “simulation"
   $\rightarrow$ Mathematization and physical modelling

Modelling biochemical pathways requires paradigm shift

1. Repair medicine $\rightarrow$ Traditional health investigation
2. Drawing and labelling magnified pictures
   $\rightarrow$ Investigation of theoretically defined magnitudes
3. $\left\{\begin{array}{l}\text{Holism (}\textit{Systems biology}\text{)}\\ \text{Reductionism (e.g., material properties of }\textit{model membranes}\text{)}\end{array}\right.$
   $\rightarrow$ Confinement of single events
4. Ad-hoc fancied mechanisms (predominance of the visible, contempt of the invisible)
   $\rightarrow$ Fundamental laws (*The visible must be explained in terms of the invisible*, Y. Manin)
5. Systems of ordinary differential equations
   $\rightarrow$ Global analysis, pde, geometry
6. “Modelling" and “simulation"
   $\rightarrow$ Mathematization and physical modelling

Modelling biochemical pathways requires paradigm shift

1. Repair medicine $\rightarrow$ Traditional health investigation
2. Drawing and labelling magnified pictures
   $\rightarrow$ Investigation of theoretically defined magnitudes
3. $\left\{\begin{array}{l}\text{Holism (}\textit{Systems biology}\text{)}\\ \text{Reductionism (e.g., material properties of }\textit{model membranes}\text{)}\end{array}\right.$
   $\rightarrow$ Confinement of single events
4. Ad-hoc fancied mechanisms (predominance of the visible, contempt of the invisible)
   $\rightarrow$ Fundamental laws (*The visible must be explained in terms of the invisible*, Y. Manin)
5. Systems of ordinary differential equations
   $\rightarrow$ Global analysis, pde, geometry
6. "Modelling" and "simulation"
   $\rightarrow$ Mathematization and physical modelling

Modelling biochemical pathways requires paradigm shift

1. Repair medicine $\rightarrow$ Traditional health investigation
2. Drawing and labelling magnified pictures
   $\rightarrow$ Investigation of theoretically defined magnitudes
3. $\left\{\begin{array}{l}\text{Holism (}\textit{Systems biology}\text{)}\\ \text{Reductionism (e.g., material properties of }\textit{model membranes}\text{)}\end{array}\right.$
   $\rightarrow$ Confinement of single events
4. Ad-hoc fancied mechanisms (predominance of the visible, contempt of the invisible)
   $\rightarrow$ Fundamental laws (*The visible must be explained in terms of the invisible*, Y. Manin)
5. Systems of ordinary differential equations
   $\rightarrow$ Global analysis, pde, geometry
6. “Modelling" and “simulation"
   $\rightarrow$ Mathematization and physical modelling

Character of mathematical models in medicine

Mathematical models are different:

- Ad-hoc models
  - Predictive power when tuned properly
  - No theoretical basis
- Theoretically based models
  - Strong explanatory power
  - In science: exceptional
- Metaphors
  - Imaginative power: molecular dynamics, compartments, Maxwell
  - Totally misleading when taken literally
  - Only applicable for excluding erroneous perceptions

Character of mathematical models in medicine

Mathematical models are different:

- Ad-hoc models
  - Predictive power when tuned properly
  - No theoretical basis
- Theoretically based models
  - Strong explanatory power
  - In science: exceptional
- Metaphors
  - Imaginative power: molecular dynamics, compartments, Maxwell
  - Totally misleading when taken literally
  - Only applicable for excluding erroneous perceptions

Character of mathematical models in medicine

Mathematical models are different:

- Ad-hoc models
  - Predictive power when tuned properly
  - No theoretical basis
- Theoretically based models
  - Strong explanatory power
  - In science: exceptional
- Metaphors
  - Imaginative power: molecular dynamics, compartments, Maxwell
  - Totally misleading when taken literally
  - Only applicable for excluding erroneous perceptions

Character of mathematical models in medicine

Mathematical models are different:

- Ad-hoc models
  - Predictive power when tuned properly
  - No theoretical basis
- Theoretically based models
  - Strong explanatory power
  - In science: exceptional
- Metaphors
  - Imaginative power: molecular dynamics, compartments, Maxwell
  - Totally misleading when taken literally
  - Only applicable for excluding erroneous perceptions

Industry' questions

Industry: *What will be major applications in cellular analysis?*

1. testing cytotoxicity and vitality effects of nanoparticles and drug components;
2. testing vitality of cells in tissue for transplantation;
3. testing cell vitality where biopsy is possible;
4. testing in-vivo tissue where optical inspection (like gastroscopy or rectoscopy) is possible and suitable;
5. instrument for basic cell biology research (e.g., identifying the function, protein expression or suppression of illness supporting genes; localisation of actin filament structures; etc).

References I

eamericonbook B. Booß-Bavnbek, A. Otto, M. Pedersen, J. Shillcock (eds.),
Modeling of Membrane Processes in Animal Cells, Proceedings of a Workshop, Roskilde University, 29 June - 1 July 2006.
Special Issue, Biophysical Reviews and Letters, World Scientific, Singapore, 2007, iv + 122 pp.

eamericonbook B. Booß-Bavnbek et al. (eds.),
Systems Biology of Regulated Exocytosis in Pancreatic Beta Cells
Springer-Verlag, New York, ca. 400 pages, in print.
Drafts for inspection at http://milne.ruc.dk/ Booss/BetaSys/
Chapter on *Geometric and Electromagnetic Aspects of Fusion Pore Making* also on arXiv:0912.3738 [math.AP]

eamericonarticle P. Rorsman and E. Renström,
Insulin granule dynamics in pancreatic beta cells,
Diabetologia **46** (2003): 1029–1045.

References II

eamericonarticle L. A. Caffarelli, A. Petrosyan and H. Shahgholian,
Regularity of a free boundary in parabolic potential theory,
J. Amer. Math. Soc. **17** (2004): 827–869 (electronic).

eamericonarticle A. Blanchet,
On the singular set of the parabolic obstacle problem,
J. Differential Equations **231** (2006): 656–672.

eamericonarticle G. S. Weiss,
Self-similar blow-up and Hausdorff dimension estimates for a class of parabolic free boundary problems,
SIAM J. Math. Anal. **30** (1999): 623–644 (electronic).

eamericonarticle Y. Manin,
Mathematical knowledge: internal, social and cultural aspects.
Commissioned for C. Bartocci and P. Odifreddi (eds.),
Mathematics and Culture, vol. 2, 2007, math.HO/0703427.

Appendix 1: Electro-dynamic Marking Technology

- *Capturing structure and function of the human cell*
- One emerging new technology: NP based transducer = tracing intra-cellular dynamics *in-vivo* by specially coated nanoparticles

$$\begin{pmatrix} \text{Intracellular signals} \\ \text{Vesicle dynamics} \\ \text{Organelles' geometry} \end{pmatrix} \Longrightarrow \begin{matrix} \text{High-end cell analysis} \\ \text{Test case: pancreatic } \beta\text{-cells} \\ \text{General: stem cells, neurons etc} \end{matrix}$$

1. Fine resolution (lower nano range),
2. Long time intervals for observation (up to seconds and minutes),
3. Surveying huge cell-global distances (of up to thousands of nm cell diameter) for capturing complex interaction,
4. Addressing specific organelles (like mitochondria, microtubules, actin filament, and granules),
5. Coupling with the huge already available data from genetics and proteomics (identifying the functional consequences of observed inherited, i.e., genetic deviations), and
6. Model-based design of the observations, storage and analysis of the data, and numerical simulation of possible operations.

Appendix 1: Electro-dynamic Marking Technology

- *Capturing structure and function of the human cell*
- One emerging new technology: NP based transducer = tracing intra-cellular dynamics *in-vivo* by specially coated nanoparticles

$$\begin{pmatrix} \text{Intracellular signals} \\ \text{Vesicle dynamics} \\ \text{Organelles' geometry} \end{pmatrix} \Longrightarrow \begin{matrix} \text{High-end cell analysis} \\ \text{Test case: pancreatic } \beta\text{-cells} \\ \text{General: stem cells, neurons etc} \end{matrix}$$

1. Fine resolution (lower nano range),
2. Long time intervals for observation (up to seconds and minutes),
3. Surveying huge cell-global distances (of up to thousands of nm cell diameter) for capturing complex interaction,
4. Addressing specific organelles (like mitochondria, microtubules, actin filament, and granules),
5. Coupling with the huge already available data from genetics and proteomics (identifying the functional consequences of observed inherited, i.e., genetic deviations), and
6. Model-based design of the observations, storage and analysis of the data, and numerical simulation of possible operations.

Appendix 1: Electro-dynamic Marking Technology

- *Capturing structure and function of the human cell*
- One emerging new technology: NP based transducer = tracing intra-cellular dynamics *in-vivo* by specially coated nanoparticles

$$\begin{pmatrix} \text{Intracellular signals} \\ \text{Vesicle dynamics} \\ \text{Organelles' geometry} \end{pmatrix} \Longrightarrow \begin{matrix} \text{High-end cell analysis} \\ \text{Test case: pancreatic } \beta\text{-cells} \\ \text{General: stem cells, neurons etc} \end{matrix}$$

1. Fine resolution (lower nano range),
2. Long time intervals for observation (up to seconds and minutes),
3. Surveying huge cell-global distances (of up to thousands of nm cell diameter) for capturing complex interaction,
4. Addressing specific organelles (like mitochondria, microtubules, actin filament, and granules),
5. Coupling with the huge already available data from genetics and proteomics (identifying the functional consequences of observed inherited, i.e., genetic deviations), and
6. Model-based design of the observations, storage and analysis of the data, and numerical simulation of possible operations.

Appendix 1: Electro-dynamic Marking Technology

- *Capturing structure and function of the human cell*
- One emerging new technology: NP based transducer = tracing intra-cellular dynamics *in-vivo* by specially coated nanoparticles

$$\begin{pmatrix} \text{Intracellular signals} \\ \text{Vesicle dynamics} \\ \text{Organelles' geometry} \end{pmatrix} \Longrightarrow \begin{matrix} \text{High-end cell analysis} \\ \text{Test case: pancreatic } \beta\text{-cells} \\ \text{General: stem cells, neurons etc} \end{matrix}$$

1. Fine resolution (lower nano range),
2. Long time intervals for observation (up to seconds and minutes),
3. Surveying huge cell-global distances (of up to thousands of nm cell diameter) for capturing complex interaction,
4. Addressing specific organelles (like mitochondria, microtubules, actin filament, and granules),
5. Coupling with the huge already available data from genetics and proteomics (identifying the functional consequences of observed inherited, i.e., genetic deviations), and
6. Model-based design of the observations, storage and analysis of the data, and numerical simulation of possible operations.

Appendix 1: Electro-dynamic Marking Technology

- *Capturing structure and function of the human cell*
- One emerging new technology: NP based transducer = tracing intra-cellular dynamics *in-vivo* by specially coated nanoparticles

$$\begin{pmatrix} \text{Intracellular signals} \\ \text{Vesicle dynamics} \\ \text{Organelles' geometry} \end{pmatrix} \Longrightarrow \begin{matrix} \text{High-end cell analysis} \\ \text{Test case: pancreatic } \beta\text{-cells} \\ \text{General: stem cells, neurons etc} \end{matrix}$$

1. Fine resolution (lower nano range),
2. Long time intervals for observation (up to seconds and minutes),
3. Surveying huge cell-global distances (of up to thousands of nm cell diameter) for capturing complex interaction,
4. Addressing specific organelles (like mitochondria, microtubules, actin filament, and granules),
5. Coupling with the huge already available data from genetics and proteomics (identifying the functional consequences of observed inherited, i.e., genetic deviations), and
6. Model-based design of the observations, storage and analysis of the data, and numerical simulation of possible operations.

Appendix 1: Electro-dynamic Marking Technology

- *Capturing structure and function of the human cell*
- One emerging new technology: NP based transducer = tracing intra-cellular dynamics *in-vivo* by specially coated nanoparticles

$$\begin{pmatrix} \text{Intracellular signals} \\ \text{Vesicle dynamics} \\ \text{Organelles' geometry} \end{pmatrix} \Longrightarrow \begin{matrix} \text{High-end cell analysis} \\ \text{Test case: pancreatic } \beta\text{-cells} \\ \text{General: stem cells, neurons etc} \end{matrix}$$

1. Fine resolution (lower nano range),
2. Long time intervals for observation (up to seconds and minutes),
3. Surveying huge cell-global distances (of up to thousands of nm cell diameter) for capturing complex interaction,
4. Addressing specific organelles (like mitochondria, microtubules, actin filament, and granules),
5. Coupling with the huge already available data from genetics and proteomics (identifying the functional consequences of observed inherited, i.e., genetic deviations), and
6. Model-based design of the observations, storage and analysis of the data, and numerical simulation of possible operations.

Appendix 1: Electro-dynamic Marking Technology

- *Capturing structure and function of the human cell*
- One emerging new technology: NP based transducer = tracing intra-cellular dynamics *in-vivo* by specially coated nanoparticles

$$\begin{pmatrix} \text{Intracellular signals} \\ \text{Vesicle dynamics} \\ \text{Organelles' geometry} \end{pmatrix} \Longrightarrow \begin{matrix} \text{High-end cell analysis} \\ \text{Test case: pancreatic } \beta\text{-cells} \\ \text{General: stem cells, neurons etc} \end{matrix}$$

1. Fine resolution (lower nano range),
2. Long time intervals for observation (up to seconds and minutes),
3. Surveying huge cell-global distances (of up to thousands of nm cell diameter) for capturing complex interaction,
4. Addressing specific organelles (like mitochondria, microtubules, actin filament, and granules),
5. Coupling with the huge already available data from genetics and proteomics (identifying the functional consequences of observed inherited, i.e., genetic deviations), and
6. Model-based design of the observations, storage and analysis of the data, and numerical simulation of possible operations.

Appendix 2: *In-vivo* Investigations by Dynamic Marking

- Individualized diagnosis and therapy for diabetes type 1 and 2
  1. Clarification of functional consequences of genomics and proteomics, dealing with the complications of longevity
  2. Drug component tests
- Wider scope of cellular analysis and education challenge
  1. In-vivo investigation of various microstructures (surfaces, membranes, vesicles, organelles), also in education
  2. Non-invasive handling, bio-compatibility, ethical issues
- Cross connection to information gathering in material sciences
- Impact on powder chemistry
  1. A variety of functional, inorganic NPs and nano-manipulation technology
  2. Wide range of different in vivo diagnostic and therapeutic applications as reporters or drug delivery systems
  3. Conjugation approaches and thorough investigation of nanotoxicity
- Multi-beam laser microscopy
- Software systems for the mesoscale

Appendix 2: *In-vivo* Investigations by Dynamic Marking

- Individualized diagnosis and therapy for diabetes type 1 and 2
  1. Clarification of functional consequences of genomics and proteomics, dealing with the complications of longevity
  2. Drug component tests
- Wider scope of cellular analysis and education challenge
  1. In-vivo investigation of various microstructures (surfaces, membranes, vesicles, organelles), also in education
  2. Non-invasive handling, bio-compatibility, ethical issues
- Cross connection to information gathering in material sciences
- Impact on powder chemistry
  1. A variety of functional, inorganic NPs and nano-manipulation technology
  2. Wide range of different in vivo diagnostic and therapeutic applications as reporters or drug delivery systems
  3. Conjugation approaches and thorough investigation of nanotoxicity
- Multi-beam laser microscopy
- Software systems for the mesoscale

Appendix 2: *In-vivo* Investigations by Dynamic Marking

- Individualized diagnosis and therapy for diabetes type 1 and 2
  1. Clarification of functional consequences of genomics and proteomics, dealing with the complications of longevity
  2. Drug component tests
- Wider scope of cellular analysis and education challenge
  1. In-vivo investigation of various microstructures (surfaces, membranes, vesicles, organelles), also in education
  2. Non-invasive handling, bio-compatibility, ethical issues
- Cross connection to information gathering in material sciences
- Impact on powder chemistry
  1. A variety of functional, inorganic NPs and nano-manipulation technology
  2. Wide range of different in vivo diagnostic and therapeutic applications as reporters or drug delivery systems
  3. Conjugation approaches and thorough investigation of nanotoxicity
- Multi-beam laser microscopy
- Software systems for the mesoscale

Appendix 2: *In-vivo* Investigations by Dynamic Marking

- Individualized diagnosis and therapy for diabetes type 1 and 2
  1. Clarification of functional consequences of genomics and proteomics, dealing with the complications of longevity
  2. Drug component tests
- Wider scope of cellular analysis and education challenge
  1. In-vivo investigation of various microstructures (surfaces, membranes, vesicles, organelles), also in education
  2. Non-invasive handling, bio-compatibility, ethical issues
- Cross connection to information gathering in material sciences
- Impact on powder chemistry
  1. A variety of functional, inorganic NPs and nano-manipulation technology
  2. Wide range of different in vivo diagnostic and therapeutic applications as reporters or drug delivery systems
  3. Conjugation approaches and thorough investigation of nanotoxicity
- Multi-beam laser microscopy
- Software systems for the mesoscale

Appendix 2: *In-vivo* Investigations by Dynamic Marking

- Individualized diagnosis and therapy for diabetes type 1 and 2
  1. Clarification of functional consequences of genomics and proteomics, dealing with the complications of longevity
  2. Drug component tests
- Wider scope of cellular analysis and education challenge
  1. In-vivo investigation of various microstructures (surfaces, membranes, vesicles, organelles), also in education
  2. Non-invasive handling, bio-compatibility, ethical issues
- Cross connection to information gathering in material sciences
- Impact on powder chemistry
  1. A variety of functional, inorganic NPs and nano-manipulation technology
  2. Wide range of different in vivo diagnostic and therapeutic applications as reporters or drug delivery systems
  3. Conjugation approaches and thorough investigation of nanotoxicity
- Multi-beam laser microscopy
- Software systems for the mesoscale

Appendix 2: *In-vivo* Investigations by Dynamic Marking

- Individualized diagnosis and therapy for diabetes type 1 and 2
  1. Clarification of functional consequences of genomics and proteomics, dealing with the complications of longevity
  2. Drug component tests
- Wider scope of cellular analysis and education challenge
  1. In-vivo investigation of various microstructures (surfaces, membranes, vesicles, organelles), also in education
  2. Non-invasive handling, bio-compatibility, ethical issues
- Cross connection to information gathering in material sciences
- Impact on powder chemistry
  1. A variety of functional, inorganic NPs and nano-manipulation technology
  2. Wide range of different in vivo diagnostic and therapeutic applications as reporters or drug delivery systems
  3. Conjugation approaches and thorough investigation of nanotoxicity
- Multi-beam laser microscopy
- Software systems for the mesoscale

Appendix 2: *In-vivo* Investigations by Dynamic Marking

- Individualized diagnosis and therapy for diabetes type 1 and 2
  1. Clarification of functional consequences of genomics and proteomics, dealing with the complications of longevity
  2. Drug component tests
- Wider scope of cellular analysis and education challenge
  1. In-vivo investigation of various microstructures (surfaces, membranes, vesicles, organelles), also in education
  2. Non-invasive handling, bio-compatibility, ethical issues
- Cross connection to information gathering in material sciences
- Impact on powder chemistry
  1. A variety of functional, inorganic NPs and nano-manipulation technology
  2. Wide range of different in vivo diagnostic and therapeutic applications as reporters or drug delivery systems
  3. Conjugation approaches and thorough investigation of nanotoxicity
- Multi-beam laser microscopy
- Software systems for the mesoscale

Appendix 3: Biochemical Pathway Transducer

Milestones (for case systems biology of pancreatic β-cells)

1. Theoretical preparation of a shared research agenda, along the lines of the text book effort http://milne.ruc.dk/ Booss/BetaSys/
2. Determination of maximal (and minimal) diameter of magnetic NPs to pass the plasma membrane.
3. Development of an electromagnetic processor to speed-up the transport of the magnetic NPs across the plasma membrane.
4. Integrating the dynamic marker into a laser microscope environment.
5. Development of a bundle of new NPs.
6. Model-based design of observations of cytosol fluid dynamics and organelle dynamics.
7. Development and test of a variety of antibodies.
8. Systematic check of the consequences of genetic deviations and stress for the functioning of regulated exocytosis.
9. Systematic check of the effect of various siRNA molecules and other drug components.

Appendix 3: Biochemical Pathway Transducer

Milestones (for case systems biology of pancreatic β-cells)

1. Theoretical preparation of a shared research agenda, along the lines of the text book effort http://milne.ruc.dk/ Booss/BetaSys/
2. Determination of maximal (and minimal) diameter of magnetic NPs to pass the plasma membrane.
3. Development of an electromagnetic processor to speed-up the transport of the magnetic NPs across the plasma membrane.
4. Integrating the dynamic marker into a laser microscope environment.
5. Development of a bundle of new NPs.
6. Model-based design of observations of cytosol fluid dynamics and organelle dynamics.
7. Development and test of a variety of antibodies.
8. Systematic check of the consequences of genetic deviations and stress for the functioning of regulated exocytosis.
9. Systematic check of the effect of various siRNA molecules and other drug components.

Appendix 3: Biochemical Pathway Transducer

Milestones (for case systems biology of pancreatic β-cells)

1. Theoretical preparation of a shared research agenda, along the lines of the text book effort http://milne.ruc.dk/ Booss/BetaSys/
2. Determination of maximal (and minimal) diameter of magnetic NPs to pass the plasma membrane.
3. Development of an electromagnetic processor to speed-up the transport of the magnetic NPs across the plasma membrane.
4. Integrating the dynamic marker into a laser microscope environment.
5. Development of a bundle of new NPs.
6. Model-based design of observations of cytosol fluid dynamics and organelle dynamics.
7. Development and test of a variety of antibodies.
8. Systematic check of the consequences of genetic deviations and stress for the functioning of regulated exocytosis.
9. Systematic check of the effect of various siRNA molecules and other drug components.

Appendix 3: Biochemical Pathway Transducer

Milestones (for case systems biology of pancreatic β-cells)

1. Theoretical preparation of a shared research agenda, along the lines of the text book effort http://milne.ruc.dk/ Booss/BetaSys/
2. Determination of maximal (and minimal) diameter of magnetic NPs to pass the plasma membrane.
3. Development of an electromagnetic processor to speed-up the transport of the magnetic NPs across the plasma membrane.
4. Integrating the dynamic marker into a laser microscope environment.
5. Development of a bundle of new NPs.
6. Model-based design of observations of cytosol fluid dynamics and organelle dynamics.
7. Development and test of a variety of antibodies.
8. Systematic check of the consequences of genetic deviations and stress for the functioning of regulated exocytosis.
9. Systematic check of the effect of various siRNA molecules and other drug components.

Appendix 3: Biochemical Pathway Transducer

Milestones (for case systems biology of pancreatic β-cells)

1. Theoretical preparation of a shared research agenda, along the lines of the text book effort http://milne.ruc.dk/ Booss/BetaSys/
2. Determination of maximal (and minimal) diameter of magnetic NPs to pass the plasma membrane.
3. Development of an electromagnetic processor to speed-up the transport of the magnetic NPs across the plasma membrane.
4. Integrating the dynamic marker into a laser microscope environment.
5. Development of a bundle of new NPs.
6. Model-based design of observations of cytosol fluid dynamics and organelle dynamics.
7. Development and test of a variety of antibodies.
8. Systematic check of the consequences of genetic deviations and stress for the functioning of regulated exocytosis.
9. Systematic check of the effect of various siRNA molecules and other drug components.

Appendix 3: Biochemical Pathway Transducer

Milestones (for case systems biology of pancreatic β-cells)

1. Theoretical preparation of a shared research agenda, along the lines of the text book effort http://milne.ruc.dk/ Booss/BetaSys/
2. Determination of maximal (and minimal) diameter of magnetic NPs to pass the plasma membrane.
3. Development of an electromagnetic processor to speed-up the transport of the magnetic NPs across the plasma membrane.
4. Integrating the dynamic marker into a laser microscope environment.
5. Development of a bundle of new NPs.
6. Model-based design of observations of cytosol fluid dynamics and organelle dynamics.
7. Development and test of a variety of antibodies.
8. Systematic check of the consequences of genetic deviations and stress for the functioning of regulated exocytosis.
9. Systematic check of the effect of various siRNA molecules and other drug components.

Appendix 3: Biochemical Pathway Transducer

Milestones (for case systems biology of pancreatic β-cells)

1. Theoretical preparation of a shared research agenda, along the lines of the text book effort http://milne.ruc.dk/ Booss/BetaSys/
2. Determination of maximal (and minimal) diameter of magnetic NPs to pass the plasma membrane.
3. Development of an electromagnetic processor to speed-up the transport of the magnetic NPs across the plasma membrane.
4. Integrating the dynamic marker into a laser microscope environment.
5. Development of a bundle of new NPs.
6. Model-based design of observations of cytosol fluid dynamics and organelle dynamics.
7. Development and test of a variety of antibodies.
8. Systematic check of the consequences of genetic deviations and stress for the functioning of regulated exocytosis.
9. Systematic check of the effect of various siRNA molecules and other drug components.

Appendix 3: Biochemical Pathway Transducer

Milestones (for case systems biology of pancreatic β-cells)

1. Theoretical preparation of a shared research agenda, along the lines of the text book effort http://milne.ruc.dk/ Booss/BetaSys/
2. Determination of maximal (and minimal) diameter of magnetic NPs to pass the plasma membrane.
3. Development of an electromagnetic processor to speed-up the transport of the magnetic NPs across the plasma membrane.
4. Integrating the dynamic marker into a laser microscope environment.
5. Development of a bundle of new NPs.
6. Model-based design of observations of cytosol fluid dynamics and organelle dynamics.
7. Development and test of a variety of antibodies.
8. Systematic check of the consequences of genetic deviations and stress for the functioning of regulated exocytosis.
9. Systematic check of the effect of various siRNA molecules and other drug components.

Appendix 3: Biochemical Pathway Transducer

Milestones (for case systems biology of pancreatic β-cells)

1. Theoretical preparation of a shared research agenda, along the lines of the text book effort http://milne.ruc.dk/ Booss/BetaSys/
2. Determination of maximal (and minimal) diameter of magnetic NPs to pass the plasma membrane.
3. Development of an electromagnetic processor to speed-up the transport of the magnetic NPs across the plasma membrane.
4. Integrating the dynamic marker into a laser microscope environment.
5. Development of a bundle of new NPs.
6. Model-based design of observations of cytosol fluid dynamics and organelle dynamics.
7. Development and test of a variety of antibodies.
8. Systematic check of the consequences of genetic deviations and stress for the functioning of regulated exocytosis.
9. Systematic check of the effect of various siRNA molecules and other drug components.

Appendix 3: Biochemical Pathway Transducer

Milestones (for case systems biology of pancreatic β-cells)

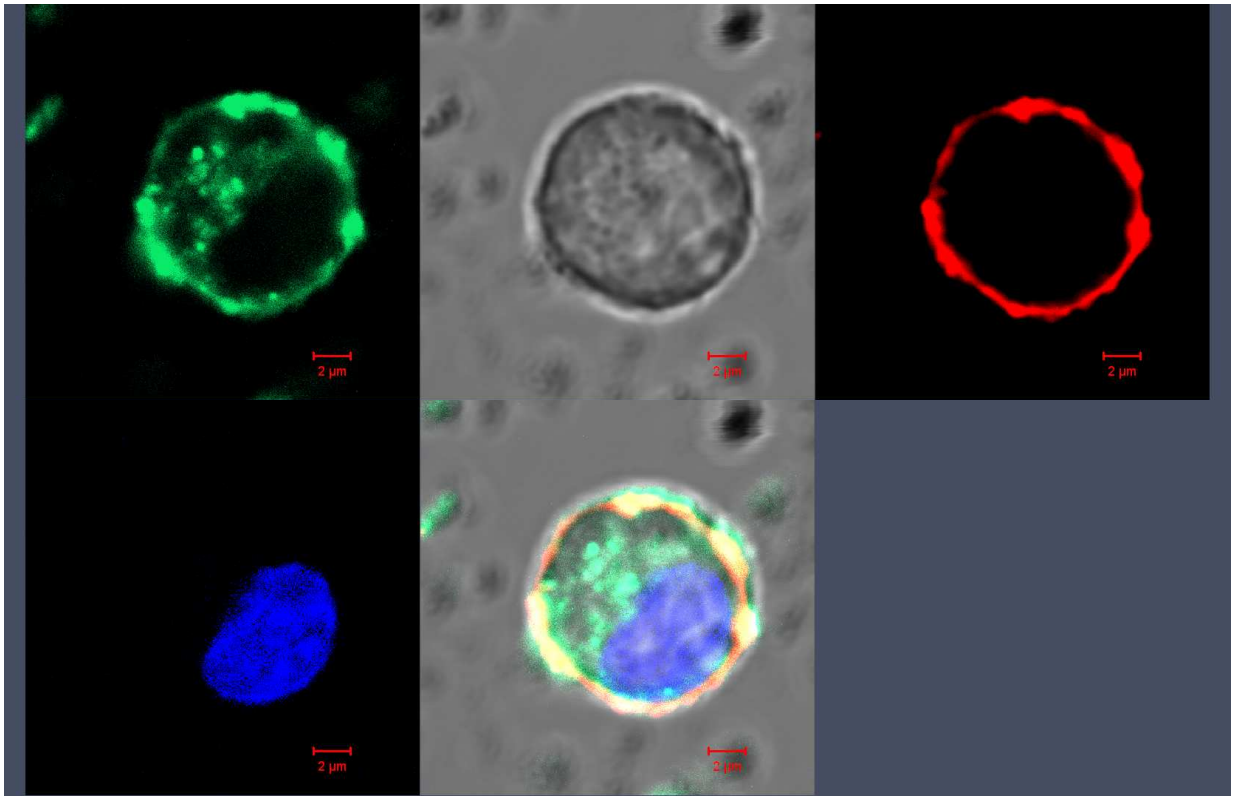
1. Theoretical preparation of a shared research agenda, along the lines of the text book effort http://milne.ruc.dk/ Booss/BetaSys/
2. Determination of maximal (and minimal) diameter of magnetic NPs to pass the plasma membrane.
3. Development of an electromagnetic processor to speed-up the transport of the magnetic NPs across the plasma membrane.
4. Integrating the dynamic marker into a laser microscope environment.
5. Development of a bundle of new NPs.
6. Model-based design of observations of cytosol fluid dynamics and organelle dynamics.
7. Development and test of a variety of antibodies.
8. Systematic check of the consequences of genetic deviations and stress for the functioning of regulated exocytosis.
9. Systematic check of the effect of various siRNA molecules and other drug components.

Appendix 4: In-vivo 5 minutes report, 100 nm beads

Break-through: successful electro-dynamic nano particle marking

NOVO-PROJECT // LUND University //STETTER-ELEKTRONIK /FK

Experiment (29-12-2009) with 100nm Beads /micromod CLD



Cell-Type : Insulin secreting cells (Ins-1)

Beads Nucleus