Óbudai Egyetem

Pro Scientia et Futuro

I want to work. For it is battle enough
Having a past such as this to confess...

citation from Attila József: “By the Danube”
A. DeGaetano DHC acceptance talk

Modelling, estimation and control

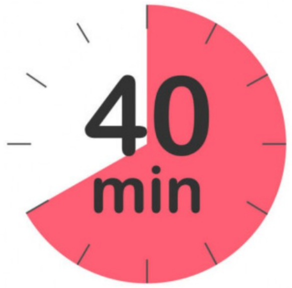
Andrea De Gaetano

IRIB CNR
INSTITUTE FOR BIOMEDICAL RESEARCH AND INNOVATION
NATIONAL RESEARCH COUNCIL (CNR)

IASI
BioMatLab
www.biomatematica.it

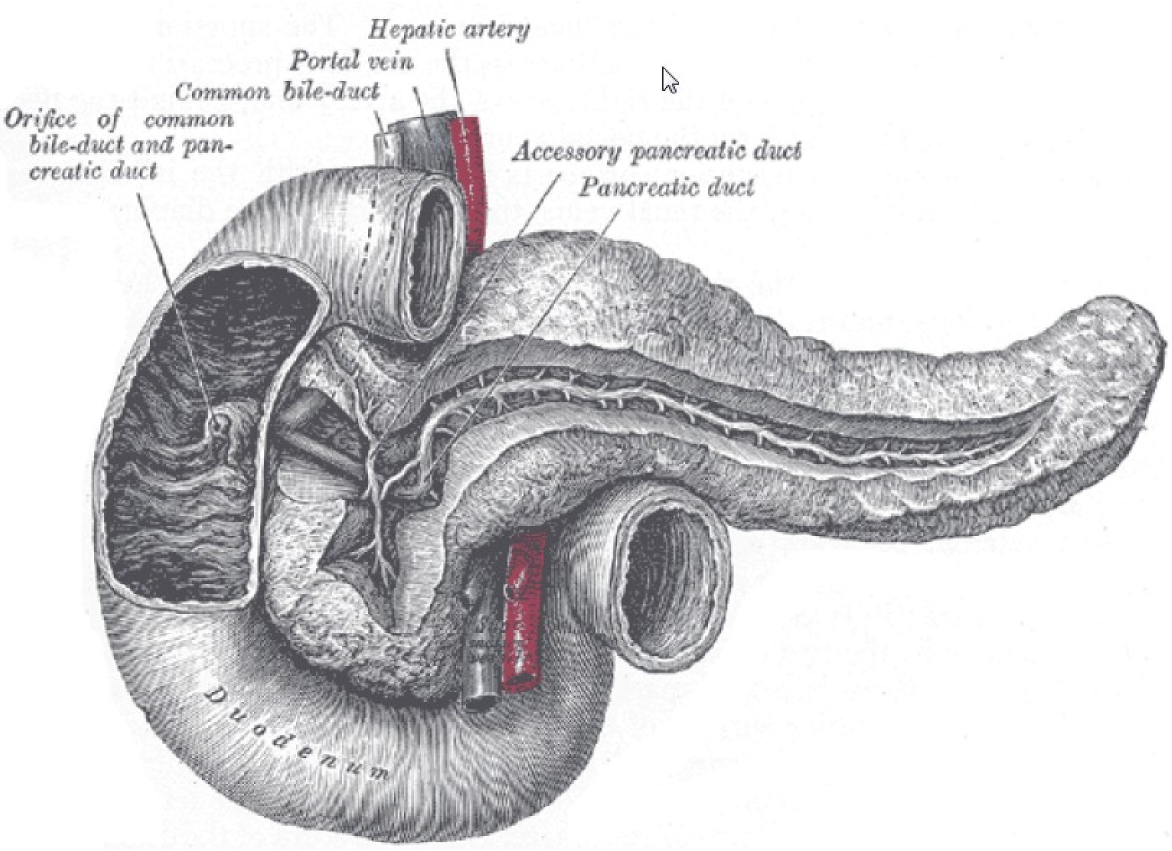
Plan of the talk:

- two stories
- a quick overview of 35 years
- the future
- conclusion: M, E & C

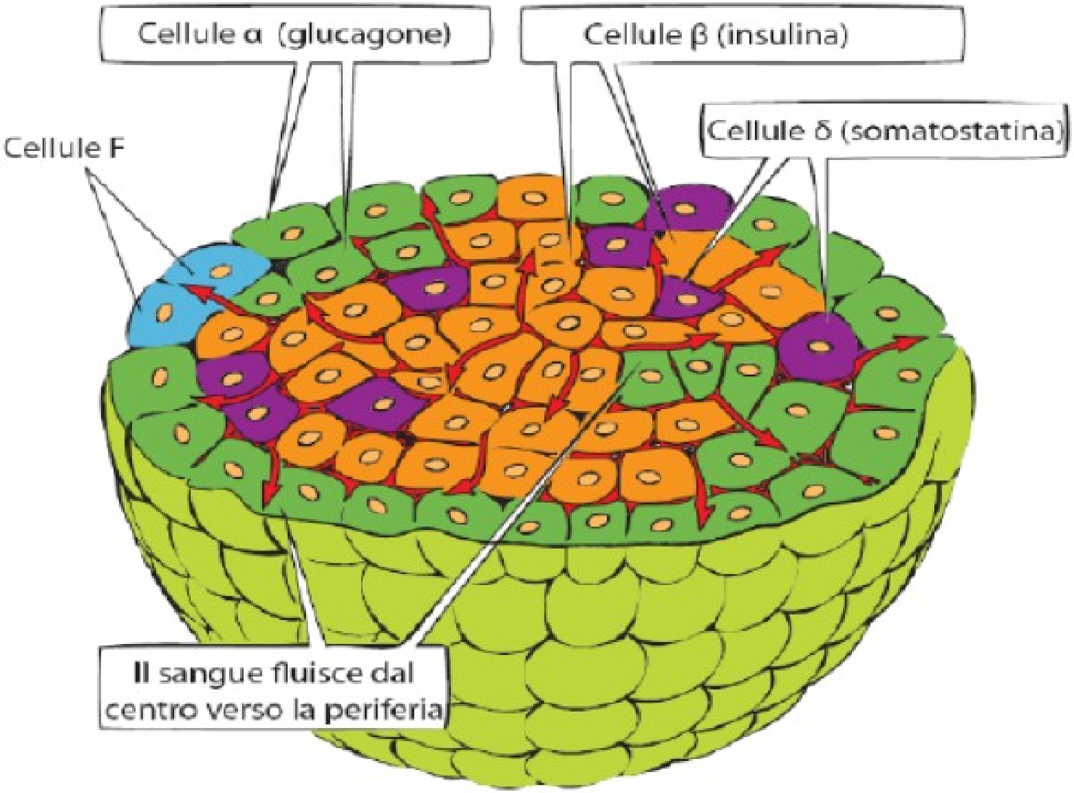


two stories
(20 minutes)

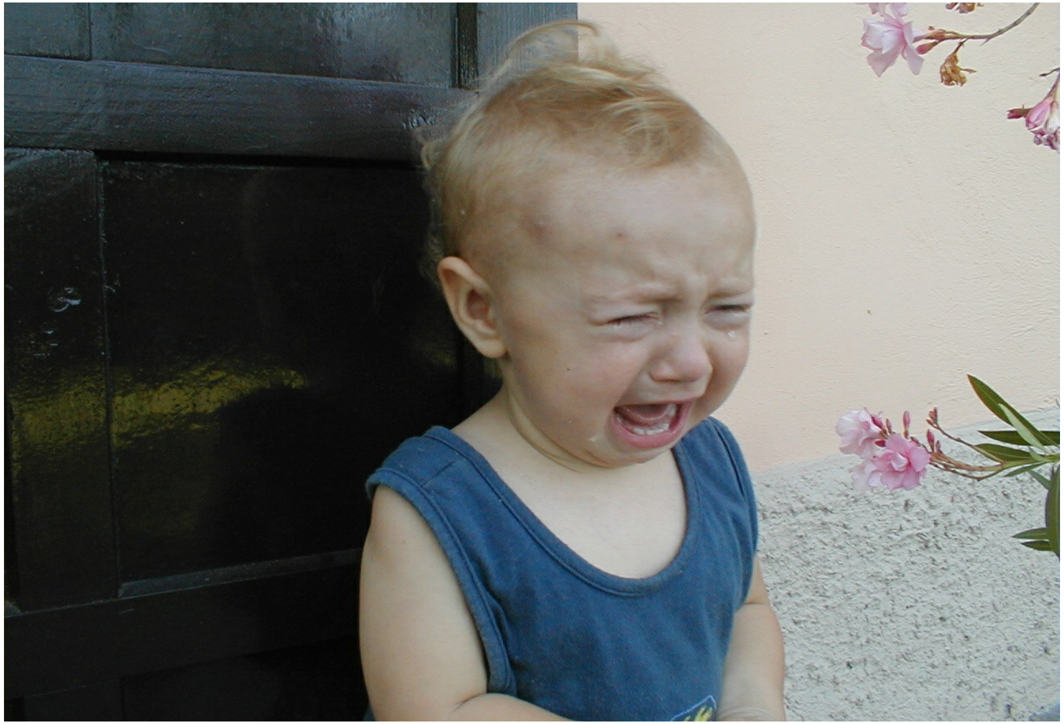
the Pancreas

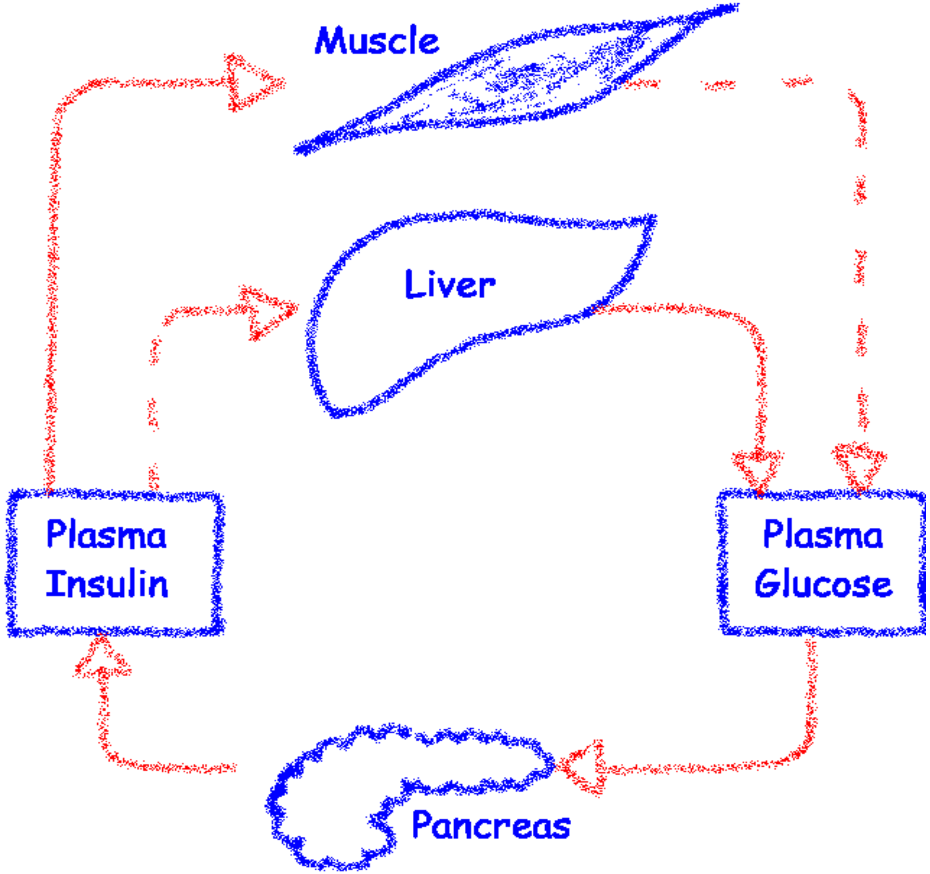


Langerhan’s Islets

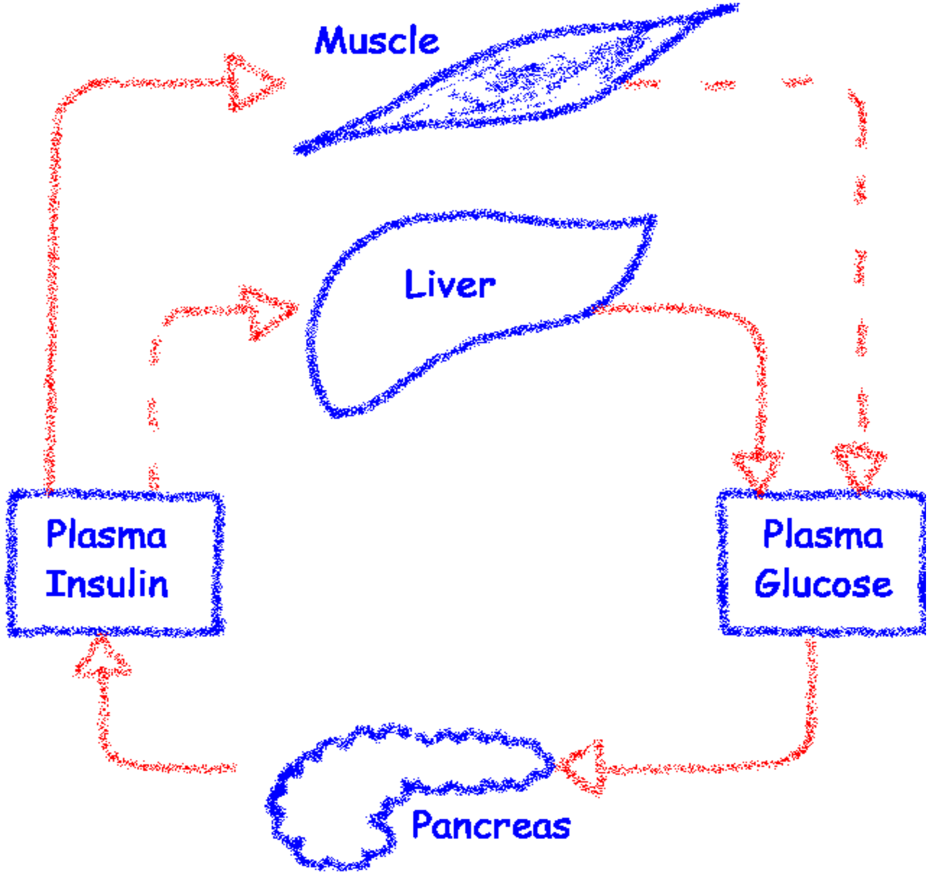


the glucose-insulin control system





successful control



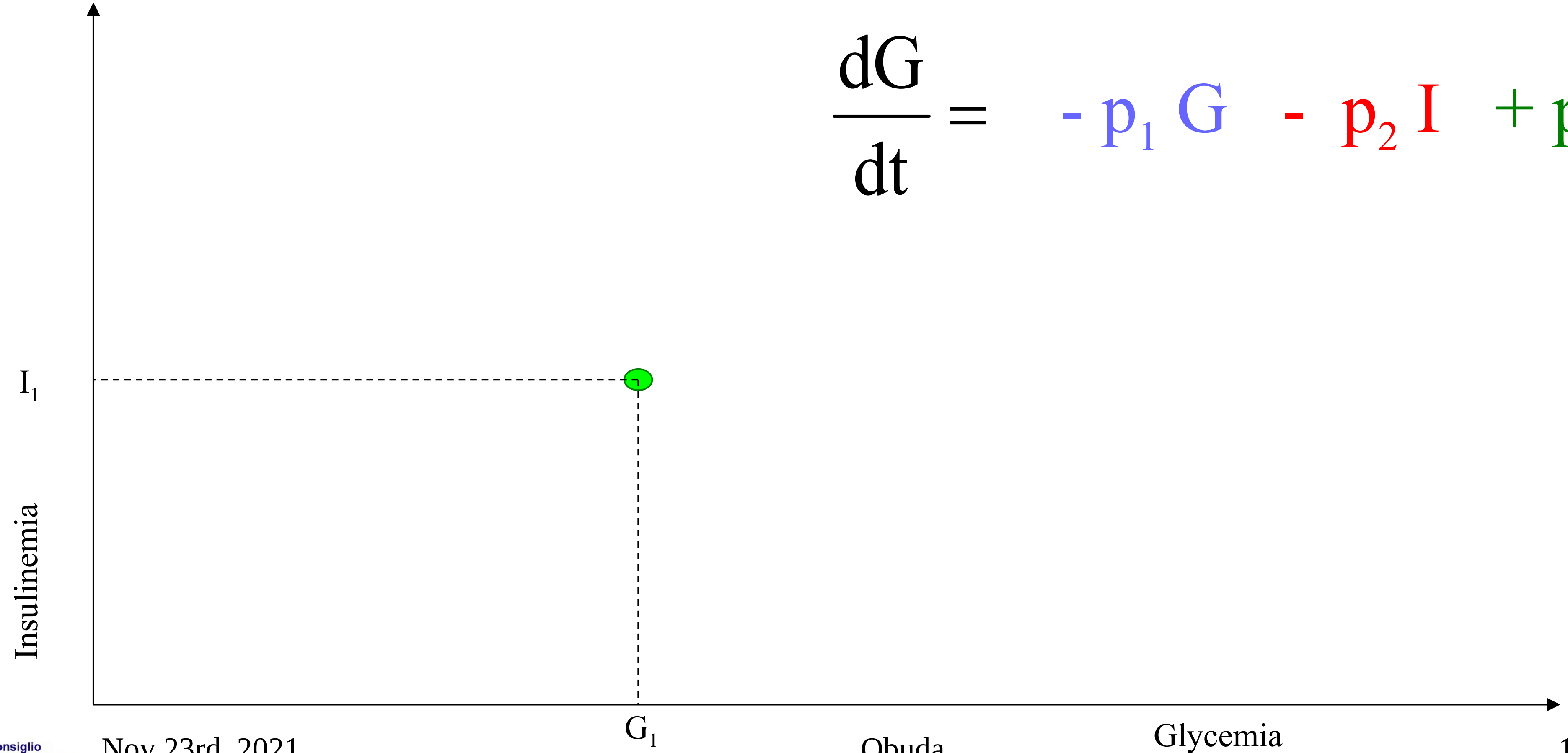
Bolie 1961

- First attempt to understand actual time-concentration points in plasma.

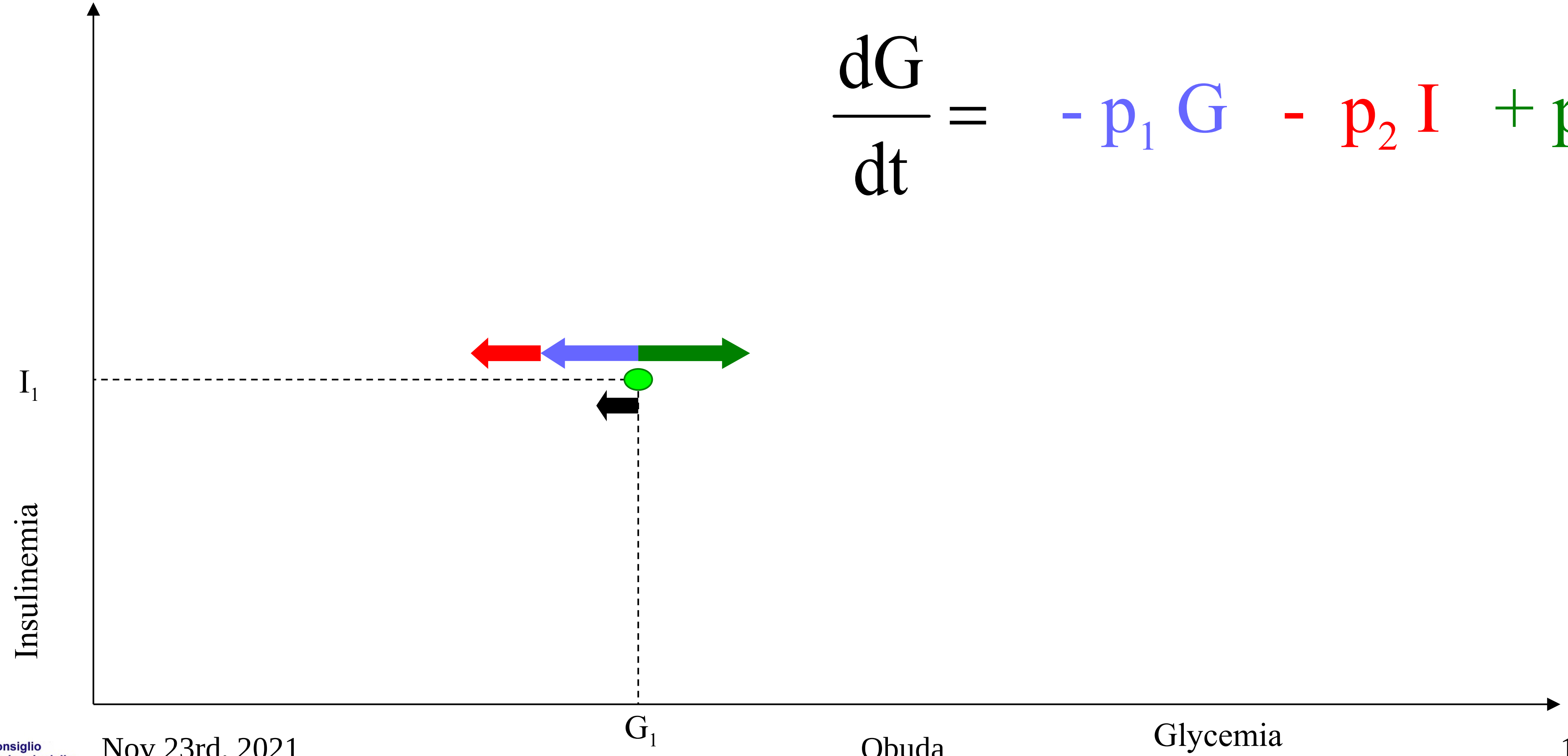
$$\frac{dG}{dt} = p_1 G + p_2 I(t) + p_3, \quad G(0) = G_0$$

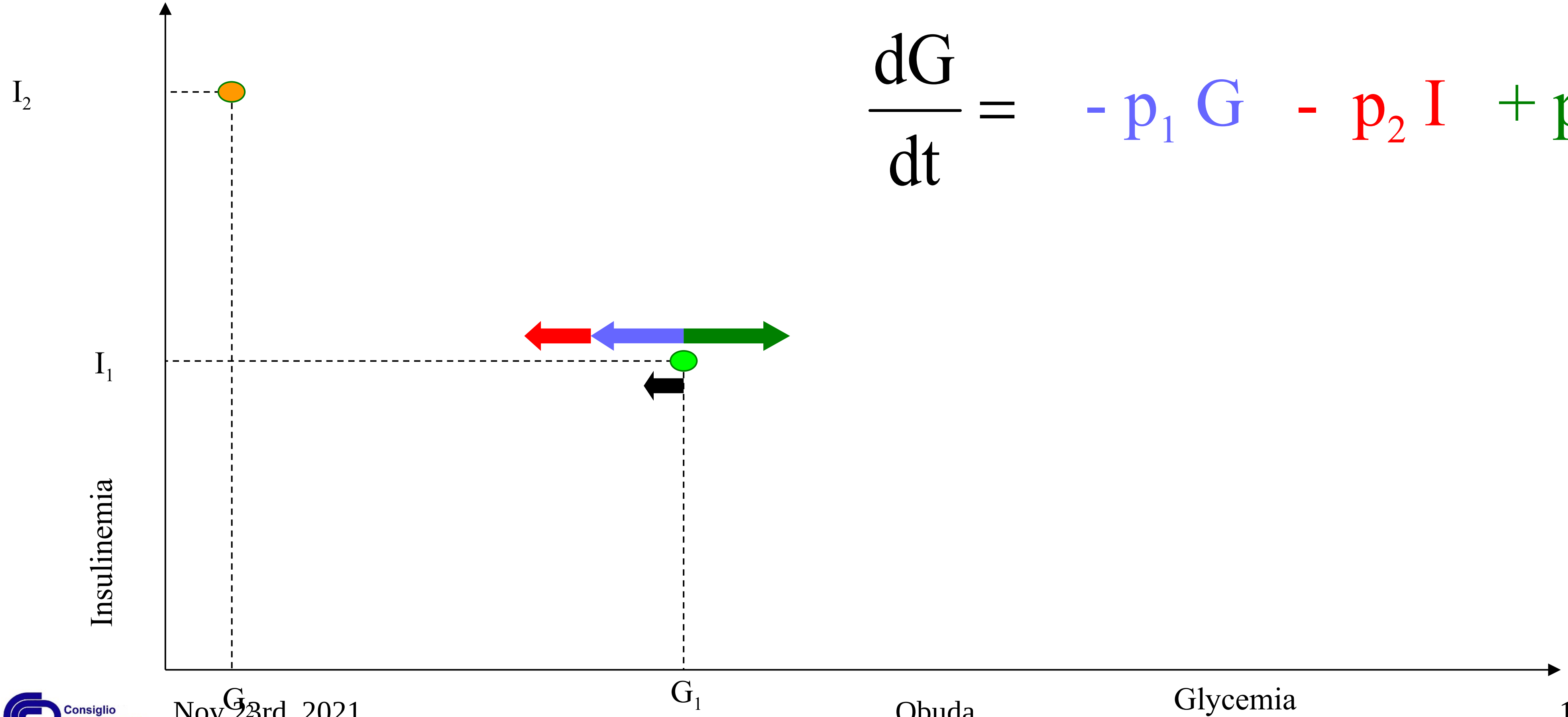
- Introduces plasma insulin and HGO
- Problems?

$$\frac{dG}{dt} = -p_1 G - p_2 I + p_3$$



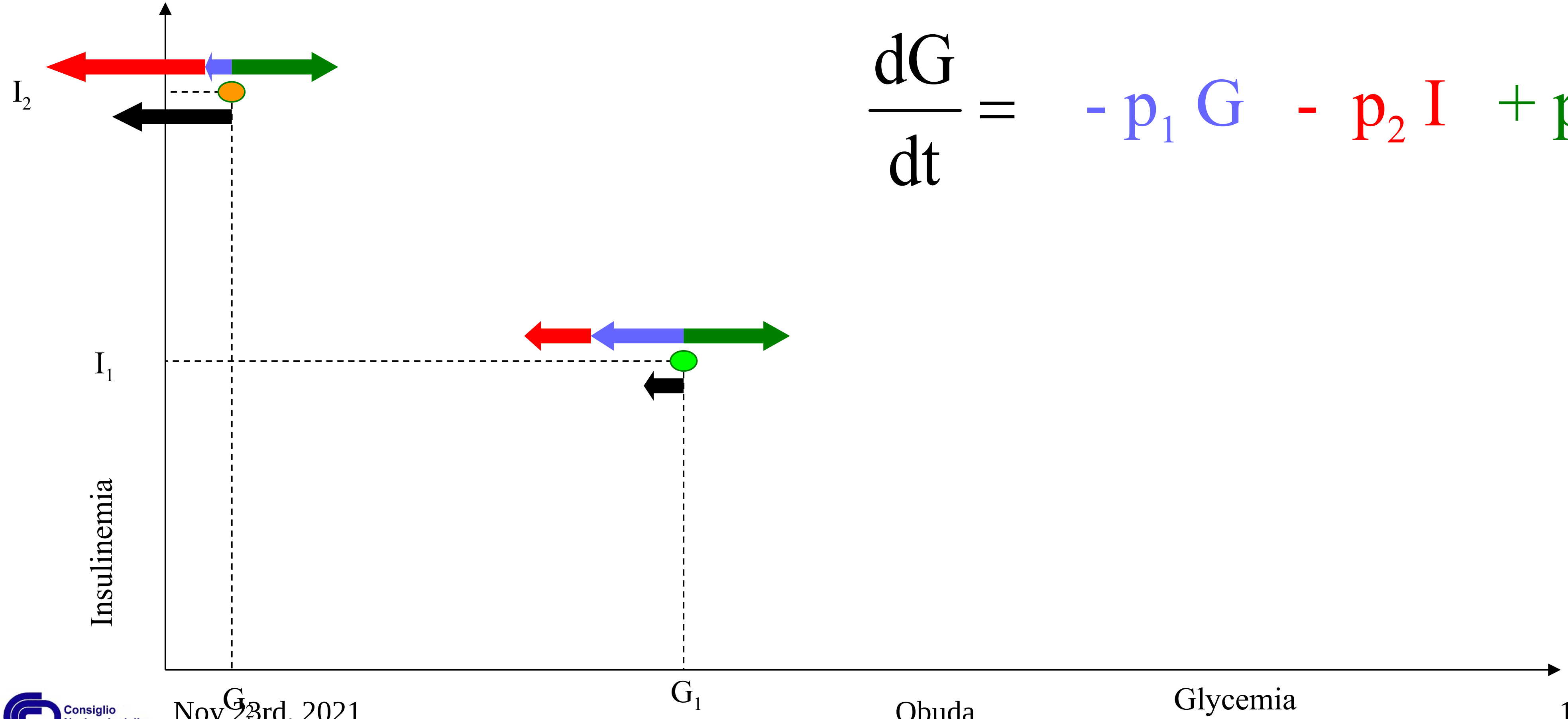
$$\frac{dG}{dt} = -p_1 G - p_2 I + p_3$$





$$\frac{dG}{dt} = -p_1 G - p_2 I + p_3$$

$$\frac{dG}{dt} = -p_1 G - p_2 I + p_3$$



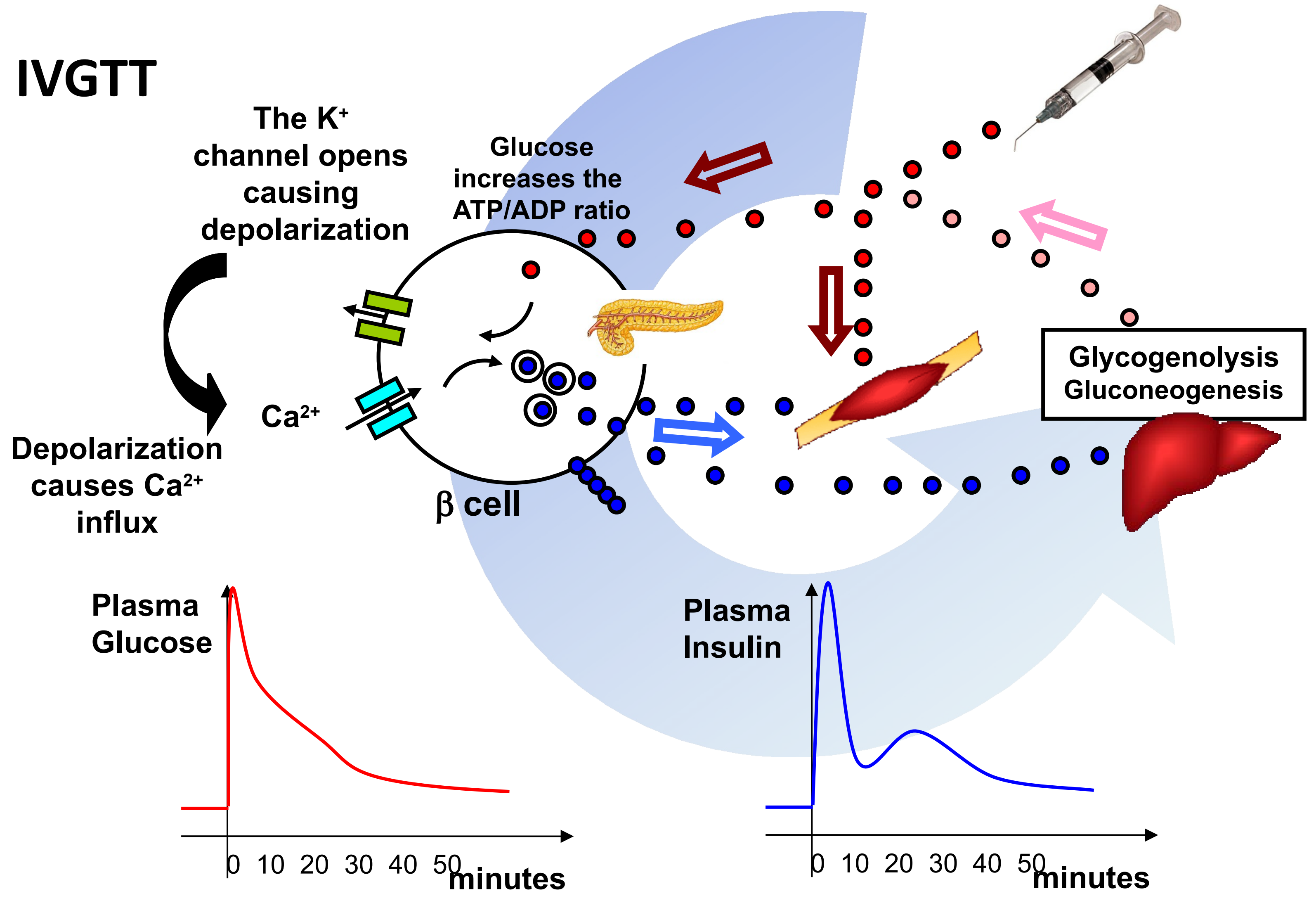
qualitative analysis reveals ...

- the actual model functional form, which allows negative solutions to appear, must have something in it which goes against the physiology as we think we know it

- Bolie: no matter how little glucose there is in blood, by increasing insulin we would be able to make the tissues extract as much more as we wanted, linearly with insulin levels.

- Mechanism seems wrong. Better to **change model**.

Perturbation experiments


IVGTT
The K+ channel opens causing depolarization
Glucose increases the ATP/ADP ratio
Ca2+
Depolarization causes Ca2+ influx
β cell
Glycogenolysis
Gluconeogenesis
Plasma Glucose
0 10 20 30 40 50
minutes
Plasma Insulin
0 10 20 30 40 50
minutes

MM 1979/1981

$$\frac{dG(t)}{dt} = -\left[b_1 + X(t)\right]G(t) + b_1 G_b, \qquad G(0) = b_0$$

$$\frac{dX(t)}{dt} = -b_2 X(t) + b_3\left[I(t) - I_b\right], \qquad X(0) = 0$$

$$\frac{dI(t)}{dt} = b_4\left[G(t) - b_5\right]^+ t - b_6\left[I(t) - I_b\right], \qquad I(0) = b_7 + I_b$$

MM 1979/1981

$$\frac{dG(t)}{dt} = -\left[b_1 + X(t)\right]G(t) + b_1 G_b, \qquad G(0) = b_0$$

$$\frac{dX(t)}{dt} = -b_2 X(t) + b_3\left[I(t) - I_b\right], \qquad X(0) = 0$$

$$\frac{dI(t)}{dt} = b_4\left[G(t) - b_5\right]^{+} t - b_6\left[I(t) - I_b\right], \qquad I(0) = b_7 + I_b$$

S_I

- For **infinite time**, $S_I = b_3/b_2$

- in one third to one half of studies on obese subjects S_I cannot be estimated, due to insufficient variation of glucose decrement with insulin.

- An IVGTT obvious for insulin resistance (high constant insulin levels) yields no estimable S_I.

Structural problems

Suppose $G_b > b_5$,

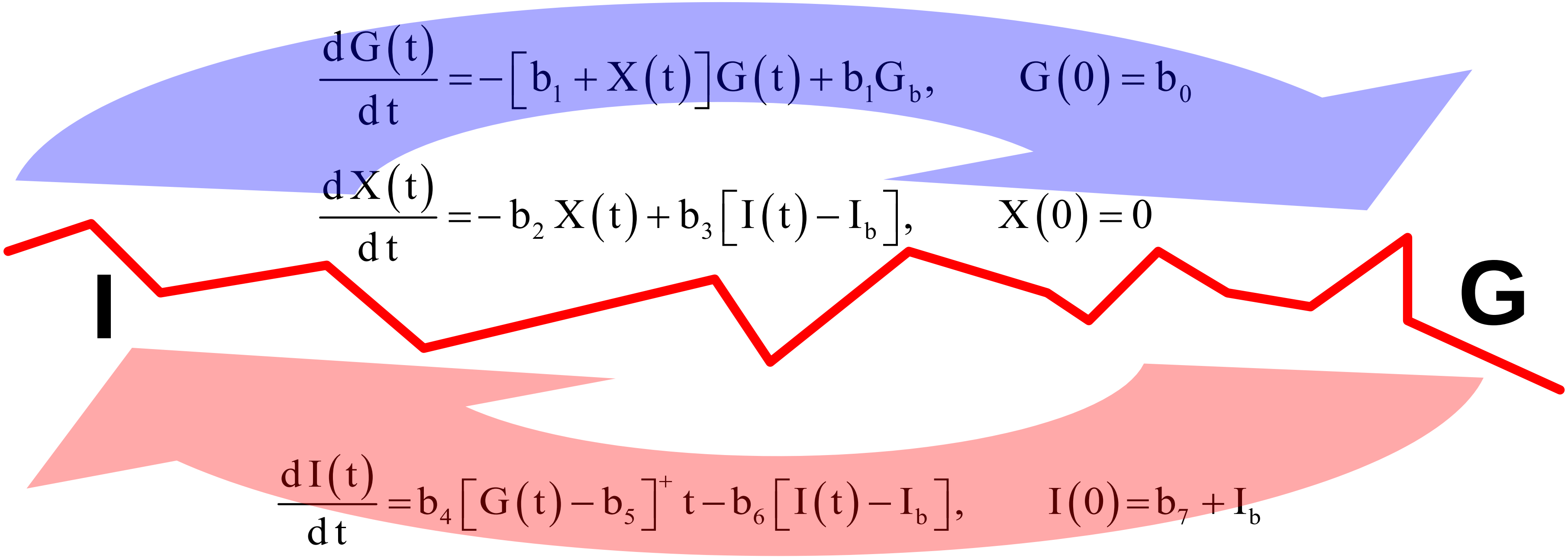
$$\limsup_{t\to\infty} G(t) > b_5$$

Then

$$\limsup_{t\to\infty} X(t) = \infty$$

In other words, for any value $b_5 < G_b$ the system does not admit an equilibrium.

Estimation problems



$$\frac{dG(t)}{dt} = -\left[b_1 + X(t)\right]G(t) + b_1 G_b, \qquad G(0) = b_0$$

$$\frac{dX(t)}{dt} = -b_2 X(t) + b_3\left[I(t) - I_b\right], \qquad X(0) = 0$$

$$\frac{dI(t)}{dt} = b_4\left[G(t) - b_5\right]^+ t - b_6\left[I(t) - I_b\right], \qquad I(0) = b_7 + I_b$$

The SDM

$$\frac{dG(t)}{dt} = -K_{xgI}\, I(t) G(t) + \frac{T_{gh}}{V_g}$$

$$\frac{dI(t)}{dt} = -K_{xi}\, I(t) + \frac{T_{ig\max}}{V_i} \frac{\left(\frac{G(t-\tau_g)}{G^*}\right)^{\gamma}}{1+\left(\frac{G(t-\tau_g)}{G^*}\right)^{\gamma}}$$

$$G(t) \equiv G_b \;\; \forall\; t \in (-\infty, 0) \;,\;\; G(0) = G_b + G_\Delta, \;\; \text{where} \;\; G_\Delta = \frac{D_g}{V_g}$$

$$I(0) = I_b + I_{\Delta G}\, G_\Delta$$

The SDM

$$\frac{dG(t)}{dt} = -K_{xgI} I(t) G(t) + \frac{T_{gh}}{V_g}$$

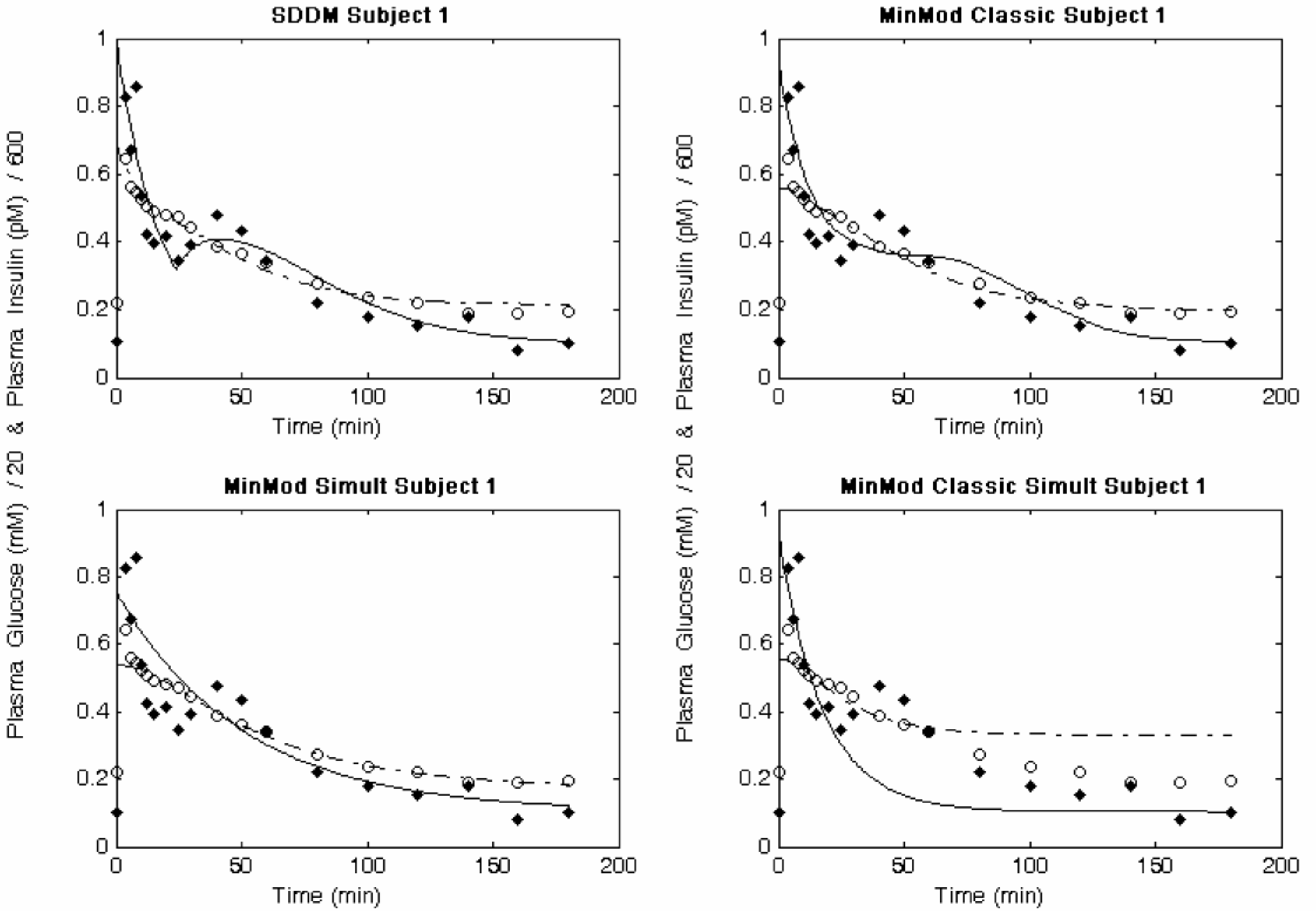
$$\frac{dI(t)}{dt} = -K_{xi} I(t) + \frac{T_{ig\max}}{V_i} \frac{\left(\frac{G(t-\tau_g)}{G^*}\right)^{\gamma}}{1+\left(\frac{G(t-\tau_g)}{G^*}\right)^{\gamma}}$$

$$G(t) \equiv G_b \;\; \forall\, t \in (-\infty, 0) \;,\;\; G(0) = G_b + G_\Delta, \;\; \text{where} \;\; G_\Delta = \frac{D_g}{V_g}$$

$$I(0) = I_b + I_{\Delta G} G_\Delta$$

SDM characteristics

- Single locally attractive equilibrium at baseline
- Positive, limited solutions
- Global stability guaranteed under conditions on parameters
- Physiologically limited pancreatic secretion ability
- Single pass GLS estimation



SDDM Subject 1
MinMod Classic Subject 1
MinMod Simult Subject 1
MinMod Classic Simult Subject 1
Plasma Glucose (mM) / 20 & Plasma Insulin (pM) / 600
Time (min)

SDM vs. MM

- 74 IVGTTs from lean (19), overweight (22), obese (22) and morbidly obese (11) subjects
- K_{xgI} from the SDM
  - identifiable (CV < 52%) in 73 out of 74 subjects (one 68%)
  - **All** estimates within physiological limits (1.25×10^{-5} to 4.36×10^{-4})
- S_I from the MM
  - not identifiable in 36 subjects out of 74, with coefficients of variation ranging from 52.76 % to $2.36 \times 10^{+9}$ %
  - in 11 subjects estimates doubtfully large (from 3.99 to 890)
  - in 8 subjects estimates very small ($\leq 1.5 \times 10^{-6}$, "zero-S_I")

second story: strange insulin secretion

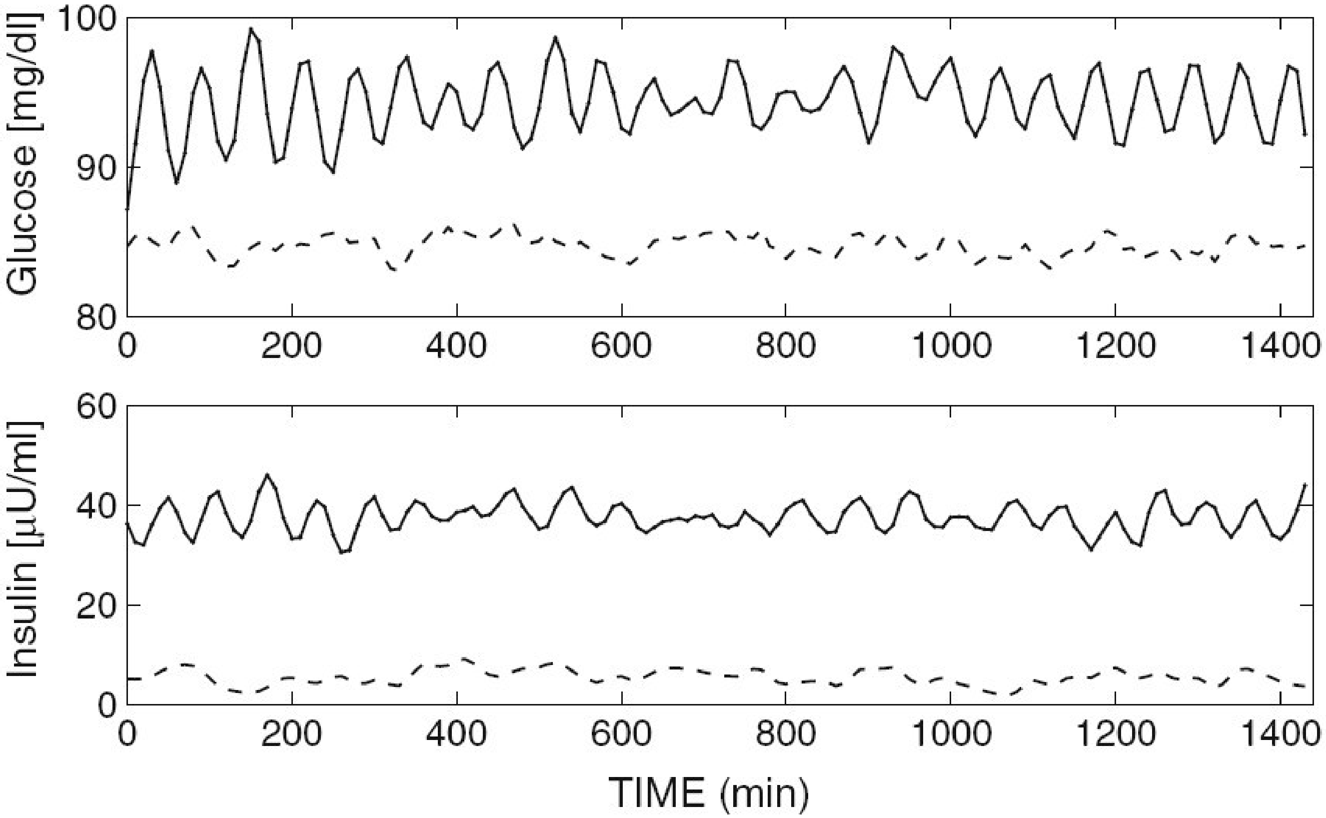
- “Synchronized”   ???
- Ex-vivo glucose perturbation experiments
  (Grodsky 1970’s, Sturis, Porksen, Simon,...)
  - constant at different levels
  - pulse, micropulse, sinusoid (entrainment)
  - step, repeated pulse

2010/2014: distributed controller hypothesis

- Many (>100K) independent controllers (islets?)
- coupling ONLY through glycemia
- fire-and-refractory (same as neurons, myocardial cells)
- slow adaptation
- GENERATING METAPARAMETERS (size of grain, refractory time, ...)

- close loop with ANY glucose dynamics

Simon



Glucose [mg/dl]
100
90
80
0
200
400
600
800
1000
1200
1400
Insulin [μU/ml]
60
40
20
0
TIME (min)

Grodsky

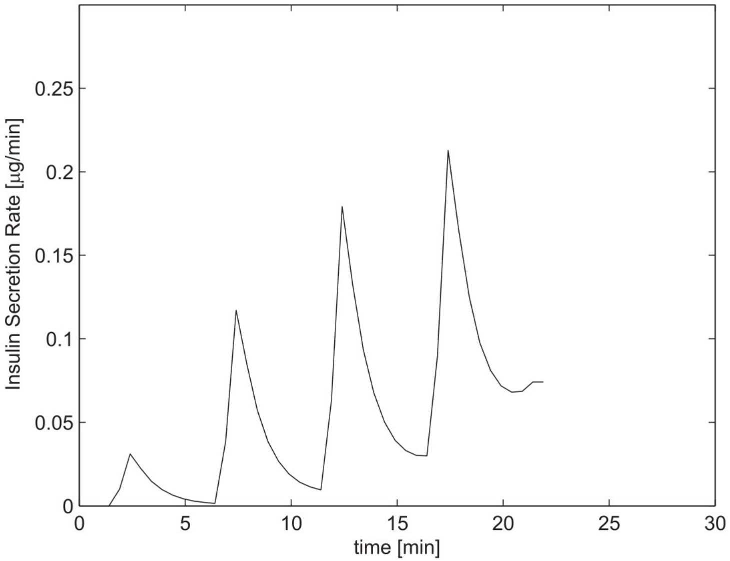
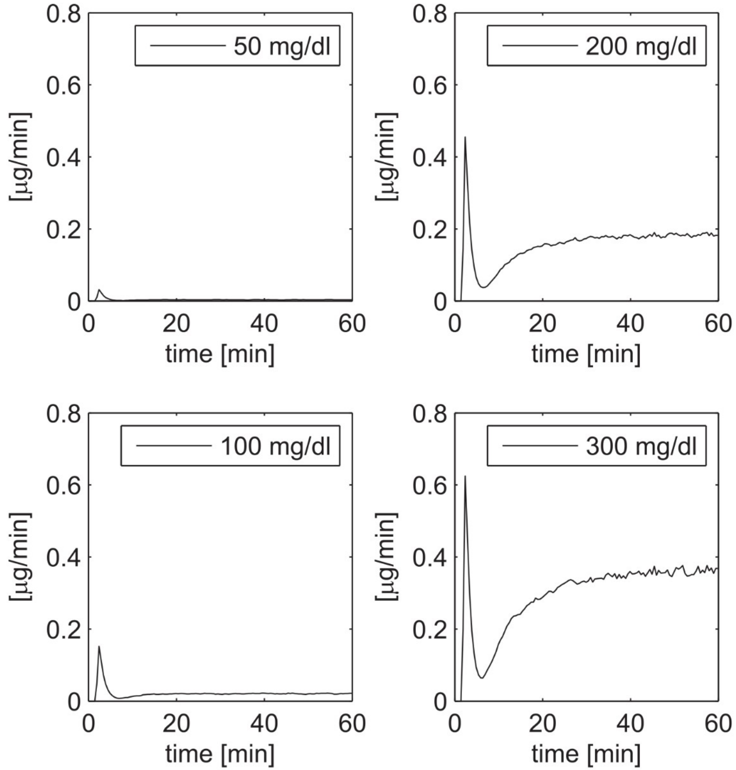


Fig 4. Insulin Secretion Rate at staircase-increasing glucose concentrations, comparable with Grodsky's first experiment (Fig 1 in [1]).



Grodsky, Sturis

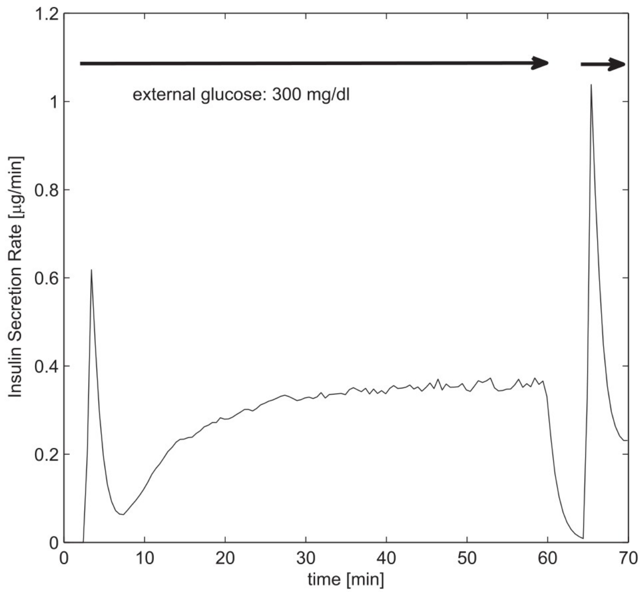


Fig 6. Insulin Secretion Rate for discontinuous constant glucose administration, comparable with Grodsky's third experiment (Fig 3 in [1]).

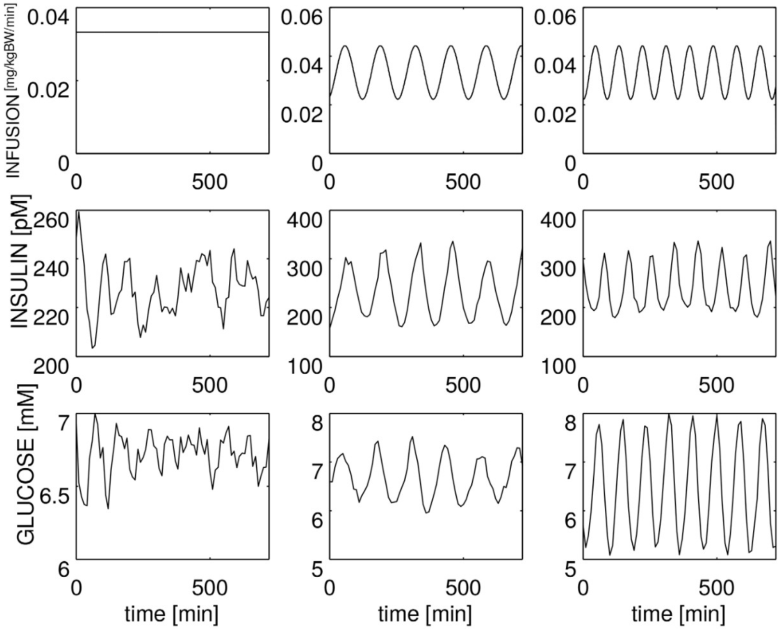


Fig 9. Glucose/insulin evolutions entrained by sinusoidal exogenous glucose administration. Glucose administration (top row), insulinemia (center row) and glycemia (bottom row) during a 720 min period. Compare this figure with Fig 1 by Sturis et al. [14].

Porksen, IVGTT

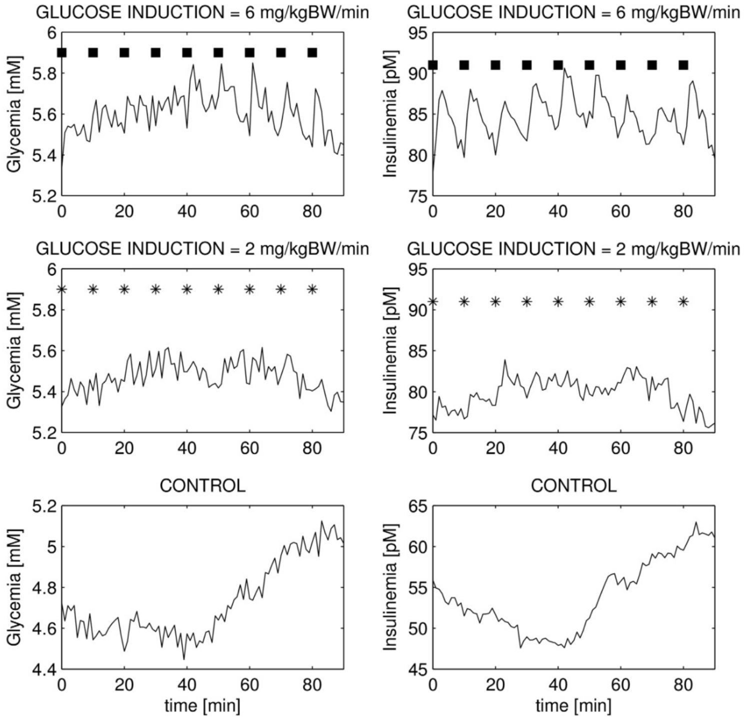


Fig 10. Glucose/insulin concentrations during high frequency minimal stimulation. Glucose (left panels) and insulin (right panels) evolution during a 1h30' period with 6 (upper panels), 2 (center panels) and 0 (lower panels) mg/kg/min intravenous glucose administration. Compare this figure with Fig 1 by Pørksen et al. [15].

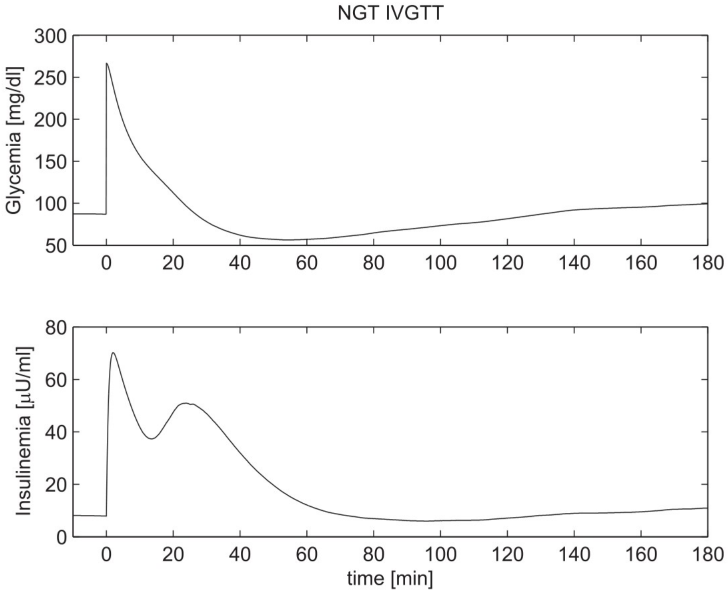


Fig 11. IVGTT experiment for an NGT patient. Simulated glycemia (upper panel) and insulinemia (lower panel) for a Normal Glucose Tolerance patient (NGT) during an Intravenous Glucose Tolerance Test (IVGTT).

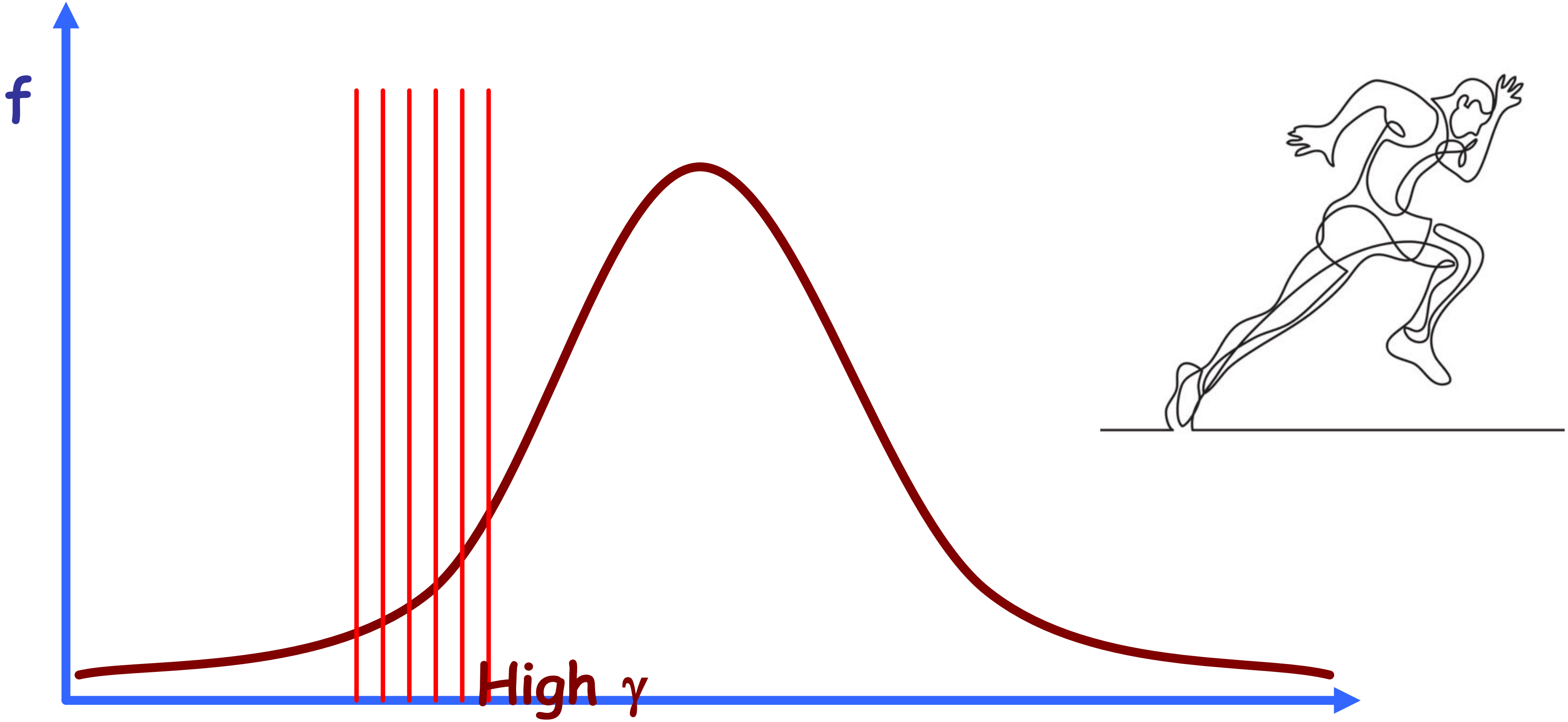
SDM revisited: why does it work?

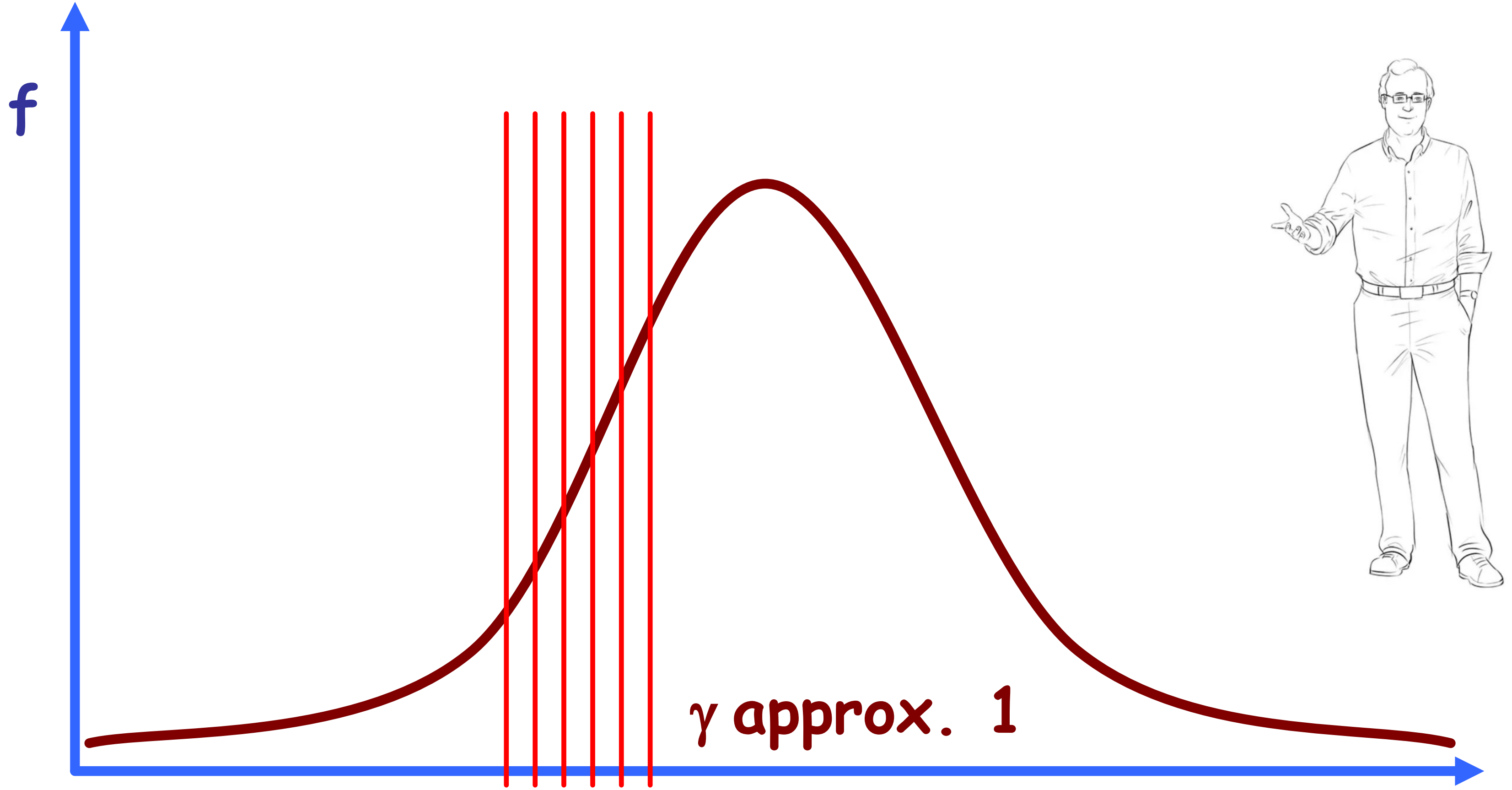
$$\frac{dG}{dt} = \frac{T_{gh}}{V_g} - K_{xgI} I G, \quad G(0) = G_b + G_\Delta$$

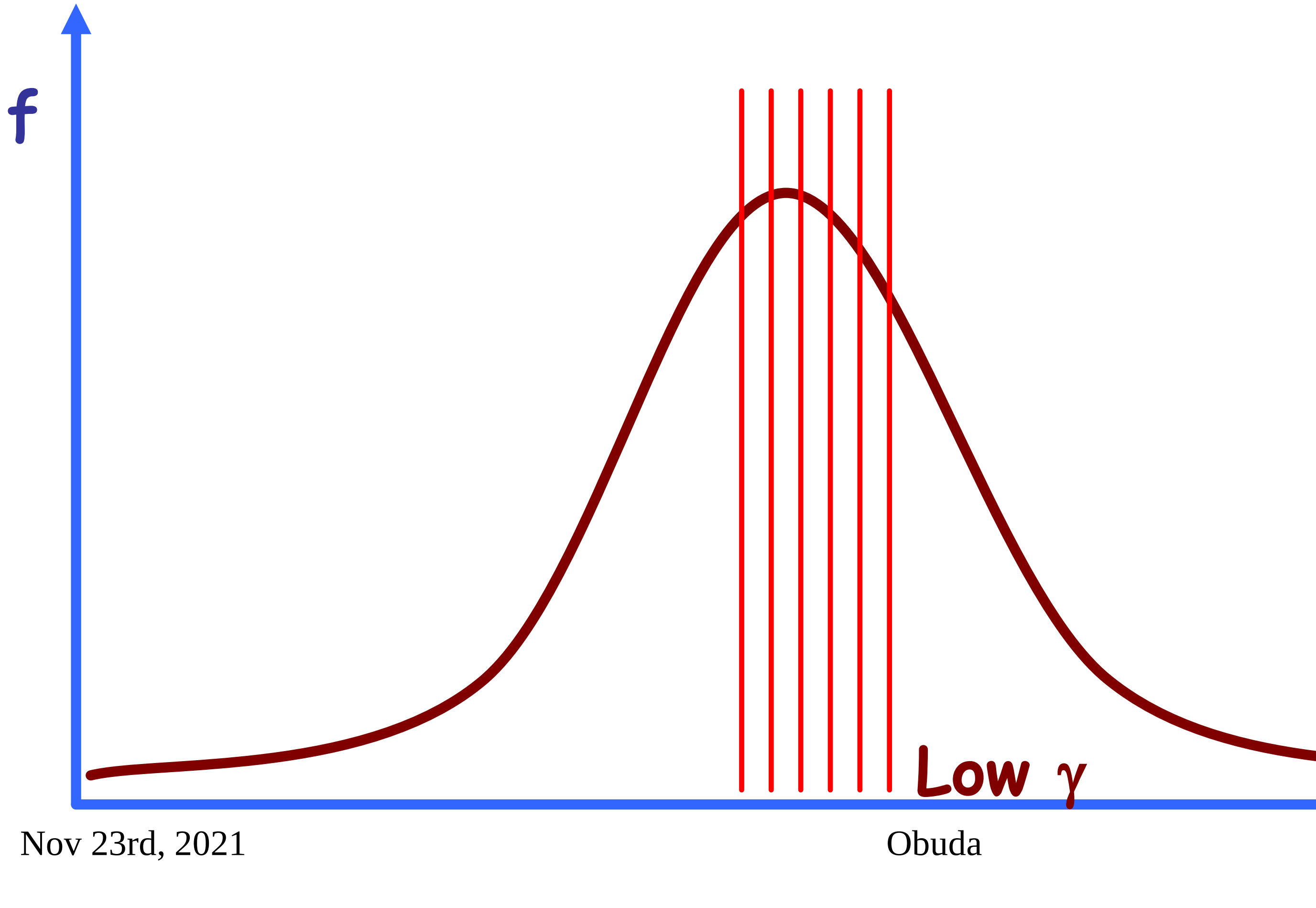
$$\frac{dI}{dt} = T_{ig}\left(\frac{G(t-\tau)}{G_b}\right)^{\gamma} - K_{xi} I, \quad I(0) = I_b + I_{\Delta G} G_\Delta$$

- ‘Glucose effectiveness’ apparently not needed
- Nonlinear exponent γ crucial for good model fit
- Distribution interpretation of γ as (related to) the derivative of the density of the thresholds?

threshold distribution interpretation



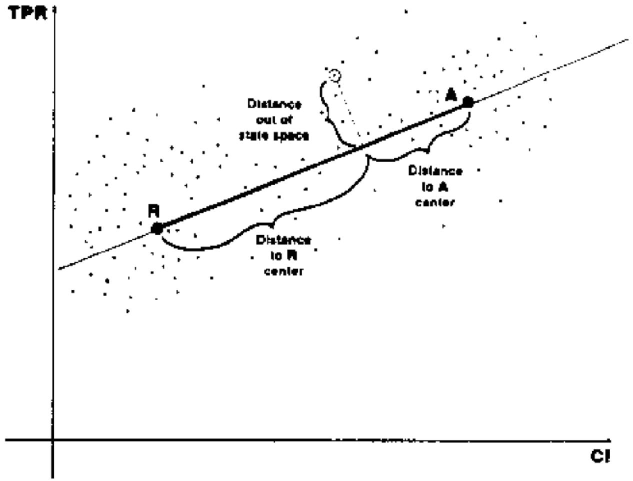

f
γ approx. 1


f
Low γ
G

A quick overview of 35 years
(5 minutes)

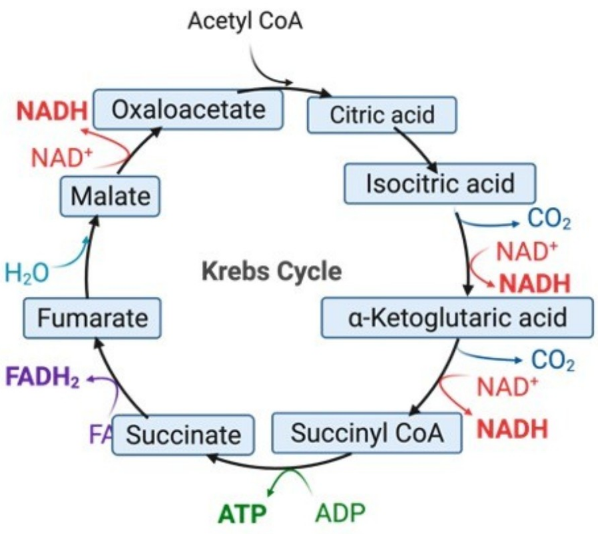
1986-1989 Baltimore: the Patient State Space

- Coleman, Siegel, Giovannini, Castagneto, Sganga, Nanni, Tacchino
- surgical ICU multi-parametric monitoring (11 original variables)
- clustering:
  - R (reference, compensated)
  - sepsis
  - metabolic/hepatic insufficiency
  - cardiovascular insufficiency
  - respiratory insufficiency



- patient trajectories & P(death) by projection onto 5-d StateSpace

1990-1999 CNR Rome: dicaboxylic acids 1/2



Linear:

$$dQ_1/dt = -k_{12}\,Q_1 + k_{21}\,Q_2$$
$$Q_1(0) = D$$
$$dQ_2/dt = k_{12}\,Q_1 - k_{21}\,Q_2 - k_{20}\,Q_2$$
$$Q_2(0) = 0$$

or

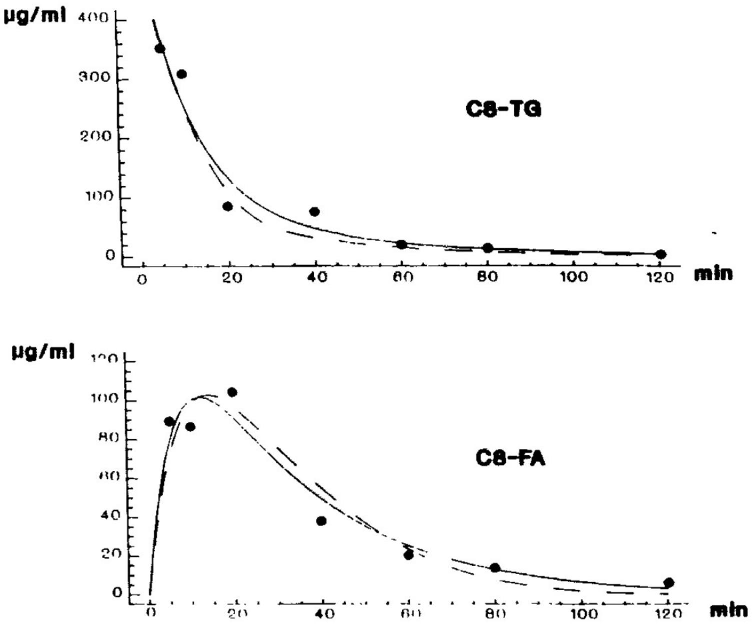
$$V_1\,dc_1/dt = -k_{12}\,c_1\,V_1 + k_{21}\,c_2\,V_2$$
$$c_1(0) = D/V_1$$
$$V_2\,dc_2/dt = k_{12}\,c_1\,V_1 - k_{21}\,c_2\,V_2 - k_{20}\,c_2\,V_2$$
$$c_2(0) = 0$$

Nonlinear:

$$V_1\,dc_1/dt = -T_{12}\,c_1/(M_{12} + c_1) + k_{21}\,c_2\,V_2$$
$$c_1(0) = D/V_1$$
$$V_2\,dc_2/dt = T_{12}\,c_1/(M_{12} + c_1) - k_{21}\,c_2\,V_2 - T_{20}\,c_2/(M_{20} + c_2)$$
$$c_2(0) = 0$$

- Mingrone, Tataranni, Raguso
- standard PK (nonlin ODE)

1990-1999 CNR Rome: dicaboxylic acids 2/2



1996 MinMod!

NONMEM improves group parameter estimation for the minimal model of glucose kinetics

ANDREA DE GAETANO, GELTRUDE MINGRONE, AND MARCO CASTAGNETO

Am.J.Physiol. 1996

- estimation!
- NONMEM -> 1985 Sheiner nlme algorithm
- Assumed MinMod

2000 MinMod?

J. Math. Biol. (2000) 40: 136–168

Journal of Mathematical Biology

Mathematical modelling of the intravenous glucose tolerance test

Andrea De Gaetano[1,★], Ovide Arino[2]

$$\frac{dG(t)}{dt} = -[p_1 + X(t)]G(t) + p_1 G_b, \qquad G(0) = p_0$$

$$\frac{dX(t)}{dt} = -p_2 X(t) + p_3[I(t) - I_b], \qquad X(0) = 0$$

$$\frac{dI(t)}{dt} = p_4[G(t) - p_5]^+ t - p_6[I(t) - I_b], \qquad I(0) = p_7 + I_b$$

$$\frac{dG(t)}{dt} = -b_1 G(t) - b_4 I(t) G(t) + b_7,$$

$$G(t) \equiv G_b \ \forall t \in [-b_5, 0), \qquad G(0) = G_b + b_0$$

$$\frac{dI(t)}{dt} = -b_2 I(t) + \frac{b_6}{b_5}\int_{t-b_5}^{t} G(s)\,ds, \qquad I(0) = I_b + b_3 b_0,$$

2000 in general: stability?

A Statistical Approach to the Determination of Stability for Dynamical Systems Modelling Physiological Processes

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URA CNRS 1204 IPRA, Pau, France

Mathematical and Computer Modelling 2000 pp 41–51

2002 in the meantime: Calorimetric Chamber

PERGAMON

Computers in Biology and Medicine 32 (2002) 297–309

Computers in Biology and Medicine

www.elsevier.com/locate/compbiomed

Computing DIT from energy expenditure measures in a respiratory chamber: a direct modeling method

S. Marino[a, *], A. De Gaetano[a], A. Giancaterini[b], D. Giordano[b], M. Manco[b], A.V. Greco[b], G. Mingrone[b]

2005/2008 / 2010 using and estimating SDE's

REVSTAT – Statistical Journal
Volume 3, Number 2, November 2005, 137–153

MIXED EFFECTS IN STOCHASTIC DIFFERENTIAL EQUATION MODELS

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Mathematical Medicine and Biology Page 1 of 15
doi:10.1093/imammb/dqn011

Maximum likelihood estimation of a time-inhomogeneous stochastic differential model of glucose dynamics

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AND

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[Received on 16 November 2007; revised on 5 March 2008; accepted on 1 April 2008]

Scandinavian Journal of Statistics, Vol. 37: 67–90, 2010
doi: 10.1111/j.1467-9469.2009.00665.x

Stochastic Differential Mixed-Effects Models

UMBERTO PICCHINI
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SUSANNE DITLEVSEN
Department of Mathematical Sciences, University of Copenhagen

2005 ... more glucose and insulin

DISCRETE AND CONTINUOUS
DYNAMICAL SYSTEMS–SERIES B
Volume **4**, Number **2**, May **2004**

Website: http://math.smsu.edu/journal

pp. **407–417**

MODELING THE INTRA-VENOUS GLUCOSE TOLERANCE TEST: A GLOBAL STUDY FOR A SINGLE-DISTRIBUTED-DELAY MODEL

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Ovide ARINO
IRD Bondy et Université de Pau, Paris, France

Toghaw *et al. Theoretical Biology and Medical Modelling* 2012, **9**:16
http://www.tbiomed.com/content/9/1/16

THEORETICAL BIOLOGY AND MEDICAL MODELLING

RESEARCH Open Access

Bariatric surgery and T2DM improvement mechanisms: a mathematical model

Puntip Toghaw[1,2,3], Alice Matone[2], Yongwimon Lenbury[3,4] and Andrea De GAETANO[2,4*]

Theoretical Biology and Medical Modelling

BioMed Central

Research Open Access

A mathematical model of the euglycemic hyperinsulinemic clamp

Umberto Picchini*[1], Andrea De Gaetano[1], Simona Panunzi[1], Susanne Ditlevsen[2] and Geltrude Mingrone[3]

Diabetologia (2006) 49:2030–2038
DOI 10.1007/s00125-006-0327-z

ARTICLE

Within-patient variation of the pharmacokinetics of subcutaneously injected biphasic insulin aspart as assessed by compartmental modelling

W. H. O. Clausen · A. De Gaetano · A. Vølund

… more glucose and insulin

OPEN ACCESS Freely available online PLOS | ONE

Routine OGTT: A Robust Model Including Incretin Effect for Precise Identification of Insulin Sensitivity and Secretion in a Single Individual

Andrea De Gaetano[1], Simona Panunzi[1]*, Alice Matone[1], Adeline Samson[2], Jana Vrbikova[3], Bela Bendlova[3], Giovanni Pacini[4]

2006 glucose and insulin: SDE's

J. Math. Biol. (2006) 53:771–796
DOI 10.1007/s00285-006-0032-z

Mathematical Biology

Modeling the euglycemic hyperinsulinemic clamp by stochastic differential equations

Umberto Picchini · Susanne Ditlevsen · Andrea De Gaetano

2007 finally a good model for the IVGTT

Theoretical Biology and Medical Modelling

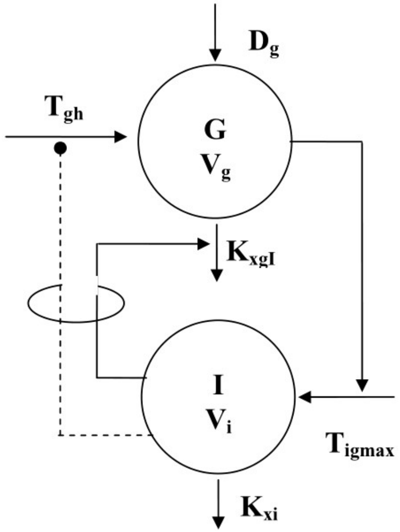
BioMed Central

Research

Open Access

A discrete Single Delay Model for the Intra-Venous Glucose Tolerance Test

Simona Panunzi*[1], Pasquale Palumbo[2] and Andrea De Gaetano[1]



DISCRETE AND CONTINUOUS
DYNAMICAL SYSTEMS–SERIES B
Volume **7**, Number **2**, March **2007**

Website: http://AIMsciences.org

pp. **399–424**

QUALITATIVE BEHAVIOR OF A FAMILY OF DELAY-DIFFERENTIAL MODELS OF THE GLUCOSE-INSULIN SYSTEM

PASQUALE PALUMBO, SIMONA PANUNZI AND ANDREA DE GAETANO

Panunzi *et al. Theoretical Biology and Medical Modelling* 2010, **7**:9
http://www.tbiomed.com/content/7/1/9

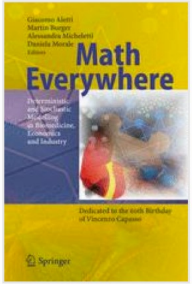
THEORETICAL BIOLOGY AND MEDICAL MODELLING

RESEARCH — Open Access

Advantages of the single delay model for the assessment of insulin sensitivity from the intravenous glucose tolerance test

Simona Panunzi[1*], Andrea De Gaetano[1], Geltrude Mingrone[2]

2007 & following: CONTROL!



Math Everywhere pp 241-252 | Cite as

State Feedback Control of the Glucose-Insulin System

Authors Authors and affiliations

Pasquale Palumbo, Andrea De Gaetano

DISCRETE AND CONTINUOUS
DYNAMICAL SYSTEMS SERIES B
Volume **12**, Number **2**, September **2009**

doi:10.3934/dcdsb.2009.12.455

pp. **455–468**

ROBUST CLOSED-LOOP CONTROL OF PLASMA GLYCEMIA: A DISCRETE-DELAY MODEL APPROACH

Proceedings of the 18th World Congress
The International Federation of Automatic Control
Milano (Italy) August 28 - September 2, 2011

IFAC

Glucose control by subcutaneous insulin administration: a DDE modelling approach

P. Palumbo * P. Pepe ** S. Panunzi * A. De Gaetano *

more control...

European Journal of Control (2012)6:591–606

DOI:10.3166/EJC.18.591–606

European Journal of Control

Time-Delay Model-Based Control of the Glucose–Insulin System, by Means of a State Observer

Pasquale Palumbo[1,*], Pierdomenico Pepe[2], Simona Panunzi[1], Andrea De Gaetano[1]

ScienceDirect

IFAC Papers Online
CONFERENCE PAPER ARCHIVE

IFAC PapersOnLine 50-1 (2017) 13526–13531

Effective Control of Glycemia using a Simple Discrete-delay Model

Claudio Gaz * Andrea De Gaetano * Costanzo Manes ** Pasquale Palumbo * Alessandro Borri * Simona Panunzi *

Luenberger-Like Observers for Nonlinear Time-Delay Systems with Application to the Artificial Pancreas

THE ATTAINMENT OF GOOD PERFORMANCE

ALESSANDRO BORRI, FILIPPO CACACE, ANDREA DE GAETANO, ALFREDO GERMANI, COSTANZO MANES, PASQUALE PALUMBO, SIMONA PANUNZI, and PIERDOMENICO PEPE

AUGUST 2017 « IEEE CONTROL SYSTEMS MAGAZINE

more control...

2017 American Control Conference
Sheraton Seattle Hotel
May 24–26, 2017, Seattle, USA

Local Sampled-Data Control of the Glucose-Insulin System

P. Pepe P. Palumbo S. Panunzi A. De Gaetano

2019 IEEE International Conference on Systems, Man and Cybernetics (SMC)
Bari, Italy, October 6-9, 2019

Rapid and ultra-rapid insulin in glycemic control

Alessandro Borri[1*], Simona Panunzi[1], Andrea De Gaetano[1]

16 IEEE TRANSACTIONS ON CONTROL SYSTEMS TECHNOLOGY, VOL. 28, NO. 1, JANUARY 2020

Semiglobal Sampled-Data Dynamic Output Feedback Controller for the Glucose–Insulin System

Mario Di Ferdinando, Pierdomenico Pepe, Pasquale Palumbo, Simona Panunzi, and Andrea De Gaetano

2008 diabetes progression

Am J Physiol Endocrinol Metab 295: E1462–E1479, 2008.
First published September 9, 2008; doi:10.1152/ajpendo.90444.2008.

Mathematical models of diabetes progression

Andrea De Gaetano,[1] Thomas Hardy,[2] Benoit Beck,[3] Eyas Abu-Raddad,[2] Pasquale Palumbo,[1] Juliana Bue-Valleskey,[2] and Niels Pørksen[2]

J. Math. Biol.
DOI 10.1007/s00285-015-0935-7

Mathematical Biology

CrossMark

A glycemia-structured population model

Alessandro Borri[1] · Simona Panunzi[1] · Andrea De Gaetano[1]

Evaluation of a Mathematical Model of Diabetes Progression Against Observations in the Diabetes Prevention Program

Thomas Hardy[1], Eyas Abu-Raddad[1], Niels Porksen[1], and Andrea De Gaetano[2]

Data-Driven Modeling of Diabetes Progression

Andrea DeGaetano, Simona Panunzi, Pasquale Palumbo, Claudio Gaz and Thomas Hardy

V. Marmarelis and G. Mitsis (eds.), *Data-driven Modeling for Diabetes*, Lecture Notes in Bioengineering, DOI: 10.1007/978-3-642-54464-4_8,

A novel fast-slow model of diabetes progression: Insights into mechanisms of response to the interventions in the Diabetes Prevention Program

PLOS | ONE

Andrea De Gaetano[1]*, Thomas Andrew Hardy[2]

2010/2014: a distributed controller theory

J. Math. Biol. (2010) 61:171–205
DOI 10.1007/s00285-009-0297-0

Mathematical Biology

An islet population model of the endocrine pancreas

Pasquale Palumbo · Andrea De Gaetano

A Unifying Organ Model of Pancreatic Insulin Secretion

Andrea De Gaetano[1], Claudio Gaz[1,2]*, Pasquale Palumbo[1], Simona Panunzi[1]

PLOS | ONE

2019...: compact is small distributed

Consistency of compact and extended models of glucose-insulin homeostasis: The role of variable pancreatic reserve

PLOS | ONE

Andrea De Gaetano[1], Claudio Gaz[1,2*], Simona Panunzi[1]

Comparison of the generating, extended-model parameter values with the obtained compact model estimates shows that the functional form of the nonlinear insulin-secretion term, empirically found to be necessary for the compact model to satisfactorily fit clinical observations, captures the pancreatic reserve level of the simulated virtual patients.

2021...: and can make distributed smaller

Journal of Mathematical Biology (2021) 82:25
https://doi.org/10.1007/s00285-021-01575-5

Mathematical Biology

Check for updates

A quasi-equilibrium reduced model of pancreatic insulin secretion

Alessandro Borri[1] · Andrea De Gaetano[1,2]

2014... meals & control of appetite

A Simple, Realistic Stochastic Model of Gastric Emptying

Jiraphat Yokrattanasak[1,2]*, Andrea De Gaetano[3], Simona Panunzi[3], Pairote Satiracoo[1,2], Wayne M. Lawton[4], Yongwimon Lenbury[1,2]

PLOS ONE

ScienceDirect

IFAC Papers Online
CONFERENCE PAPER ARCHIVE

IFAC PapersOnLine 50-1 (2017) 11011–11016

A short-term dynamical model for ghrelin

J.G. Pires **,*** A. Borri * A. De Gaetano * C. Manes **
P. Palumbo *

DISCRETE AND CONTINUOUS
DYNAMICAL SYSTEMS SERIES B

doi:10.3934/dcdsb.2021114

A SHORT-TERM FOOD INTAKE MODEL INVOLVING GLUCOSE, INSULIN AND GHRELIN

Massimo Barnabei
High School Melchiorre Delfico
Teramo, Italy

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Jorge Guerra Pires
Centro de Desenvolvimento Tecnológico em Saúde/Oswaldo Cruz Foundation
Rio de Janeiro, Brazil

2021... meals & control of appetite

AIMS Mathematical Biosciences and Engineering

http://www.aimspress.com/journal/MBE

Research article

A mathematical model of food intake

Mantana Chudtong[1,2,*] **and Andrea De Gaetano**[1,3,4]

Journal of Biological Systems, Vol. 29, No. 3 (2021) 561–576
© World Scientific Publishing Company
DOI: 10.1142/S0218339021500091

World Scientific
www.worldscientific.com

PARAMETER ESTIMATION OF A SIMPLE, REALISTIC STOCHASTIC MODEL OF GASTRIC EMPTYING OF PELLETS UNDER FASTING CONDITIONS

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Commission on Higher Education
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pairote.sat@mahidol.ac.th

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BioMatLab (Biomathematics Laboratory)
UCSC Largo A. Gemelli 8, 00168 Rome, Italy
andrea.degaetano@cnr.it

2000-2021 modelling, modelling, modelling...

Cardiovascular Engineering: An International Journal, Vol. 4, No. 1, March 2004 (© 2004)

Direct Estimation of General Pulmonary Vascular Models From Occlusion Experiments

ANDREA DE GAETANO[*,‡] and GEORGE CREMONA[†]

Cardiovascular Engineering: An International Journal, Vol. 4, No. 2, June 2004 (© 2004)

Modeling Serum Creatinine in Septic ICU Patients

ANDREA DE GAETANO,[*,¶] GIULIANA CORTESE,[*] MORTEN GRAM PEDERSEN,[*,†] SIMONA PANUNZI,[*] UMBERTO PICCHINI,[*] and ANDREA MORELLI[‡]

2000-2021 modelling, modelling, modelling...

Am J Physiol Endocrinol Metab 289: E915–E922, 2005.
First published June 21, 2005; doi:10.1152/ajpendo.00503.2003.

Approximate linear confidence and curvature of a kinetic model of dodecanedioic acid in humans

Simona Panunzi,[1] Andrea De Gaetano,[1] and Geltrude Mingrone[2]

J Pharmacokinet Pharmacodyn (2008) 35:235–248
DOI 10.1007/s10928-008-9086-4

A general approach to the apparent permeability index

Pasquale Palumbo · Umberto Picchini · Benoît Beck · Jan van Gelder · Nathalie Delbar · Andrea DeGaetano

2000-2021 modelling, modelling, modelling...

Confronto farmacoeconomico di ziprasidone con altri antipsicotici atipici per il trattamento della schizofrenia

ANALISI ECONOMICA

Andrea Fagiolini [1], Alice Matone [2], Claudio Gaz [2], Simona Panunzi [2], Andrea De Gaetano [2]

Gaetano *et al. Theoretical Biology and Medical Modelling* 2012, **9**:18
http://www.tbiomed.com/content/9/1/18

THEORETICAL BIOLOGY AND MEDICAL MODELLING

RESEARCH Open Access

Modeling rejection immunity

Andrea De Gaetano[1*], Alice Matone[1], Annamaria Agnes[2], Pasquale Palumbo[1], Francesco Ria[3] and Sabina Magalini[2]

J Pharmacokinet Pharmacodyn
DOI 10.1007/s10928-012-9259-z

ORIGINAL PAPER

A geometrical approach to the PKPD modelling of inhaled bronchodilators

Claudio Gaz · George Cremona · Simona Panunzi · Beverley Patterson · Andrea De Gaetano

OPEN ACCESS Freely available online PLOS ONE

Mathematical Modeling of Renal Tubular Glucose Absorption after Glucose Load

Andrea De Gaetano[1], Simona Panunzi[1*], Dimitris Eliopoulos[2], Thomas Hardy[3], Geltrude Mingrone[4]

2000-2021 modelling, modelling, modelling...

PLOS | ONE

RESEARCH ARTICLE

A Stochastic Delay Differential Model of Cerebral Autoregulation

Simona Panunzi[1], Laura D'Orsi[1]*, Daniela Iacoviello[2], Andrea De Gaetano[1]

J Med Syst (2016) 40:234
DOI 10.1007/s10916-016-0599-x

SYSTEMS-LEVEL QUALITY IMPROVEMENT

Simulation of Trauma Incidents

Modelling the Evolution of Patients and Resources

Alessandro Borri[1] · Simona Panunzi[1] · Rachele Brancaleoni[2] · Daniele Gui[2] · Sabina Magalini[2] · Claudio R. Gaz[1] · Andrea De Gaetano[1]

Hindawi
Computational and Mathematical Methods in Medicine
Volume 2021, Article ID 6640638, 34 pages
https://doi.org/10.1155/2021/6640638

Hindawi

Review Article

Seven Mathematical Models of Hemorrhagic Shock

Luciano Curcio,[1] Laura D'Orsi,[2] and Andrea De Gaetano[1,2]

Manuscript submitted to
AIMS' Journals
Volume **X**, Number **0X**, XX **200X**

doi:10.3934/xx.xxxxxxx

pp. **X–XX**

PATTERN FORMATION ON A GROWING OBLATE SPHEROID. AN APPLICATION TO ADULT SEA URCHIN DEVELOPMENT

Deborah Lacitignola *

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Consiglio Nazionale delle Ricerche
90146 Palermo, Italy

the future
(15 minutes)

2021 … FDE's and CGM

Sakulrang et al. *Advances in Difference Equations* (2017) 2017:150
DOI 10.1186/s13662-017-1207-1

Advances in Difference Equations
a SpringerOpen Journal

RESEARCH Open Access

CrossMark

A fractional differential equation model for continuous glucose monitoring data

Sasikarn Sakulrang[1,2], Elvin J Moore[1,2*], Surattana Sungnul[1,2] and Andrea de Gaetano[3]

Theoretical Biology 526 (2021) 110776

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

ELSEVIER

Journal of Theoretical Biology

Check for updates

Modeling continuous glucose monitoring with fractional differential equations subject to shocks

Andrea De Gaetano[a,b], Sasikarn Sakulrang[c,d], Alessandro Borri[b,*], Dario Pitocco[e], Surattana Sungnul[c,d], Elvin J. Moore[c,d]

FD Op’s Grünwald-Letnikov

$$D_t^{GL,\alpha} f(t) = \lim_{\substack{h\to 0\\ nh=t}} \frac{1}{h^\alpha} \sum_{r=0}^{n} (-1)^r \binom{\alpha}{r} f(t-rh)$$

$$\binom{\alpha}{r} = \frac{\Gamma(\alpha+1)}{\Gamma(r+1)\Gamma(\alpha-r+1)}$$

FD Op's Caputo

$$D_t^{C,\alpha} f(t) = \frac{1}{\Gamma(m-\alpha)} \int_0^t \frac{f^{(m)}(\tau)}{(t-\tau)^{\alpha-m+1}} d\tau$$

Fractional Differential Operators

- reduce to the usual integer integro-differential operators for $\alpha = m$
- are linear for any α

$$D_t^{\alpha}\left(c_1 f_1(t) + c_2 f_2(t)\right) = c_1 D_t^{\alpha} f_1(t) + c_2 D_t^{\alpha} f_2(t), \qquad c_1, c_2 \in \mathbb{R}$$

- preserve sequential integro-differentiation

$$D_t^{\alpha_1+\alpha_2} f(t) = D_t^{\alpha_1}\left(D_t^{\alpha_2} f(t)\right), \qquad \alpha_1, \alpha_2 \in \mathbb{R}$$

FD Equations

for any chosen FD Operator may wish to solve

$$D^{\alpha} y(t) = f(t)$$

subject to some initial-value conditions.

Different FD Op's determine **DIFFERENT** solutions!

Grünwald-Letnikov and Caputo

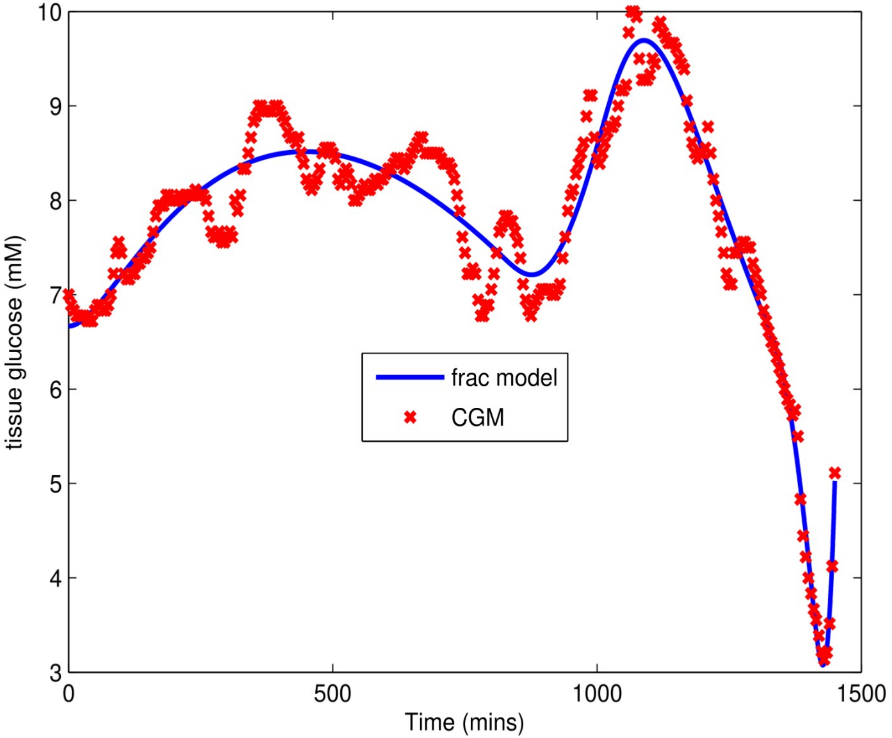
however it can be shown (Laplace transforms)

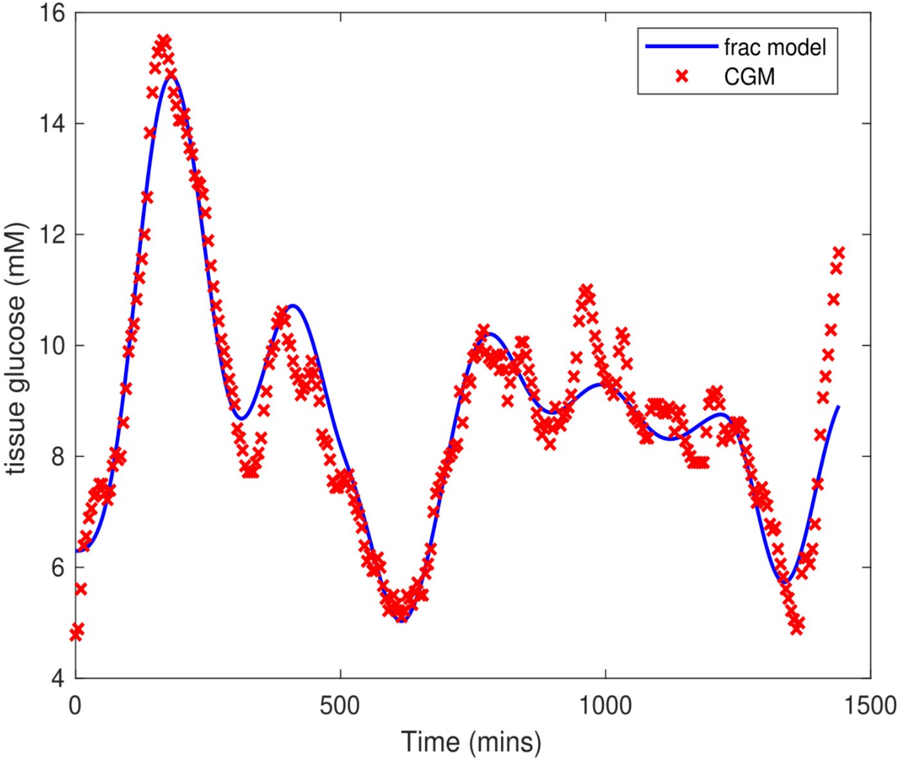
$$y^C(t) = y^{GL}(t) + \sum_{k=0}^{m-1} \frac{t^k}{k!} y^{(k)}(0)$$

$$m \in \mathbb{N}, \ 0 \leq m-1 < \alpha < m$$

- GL easy to compute
- C takes care of (INTEGER-order) initial conditions

FDE modeling example: CGM





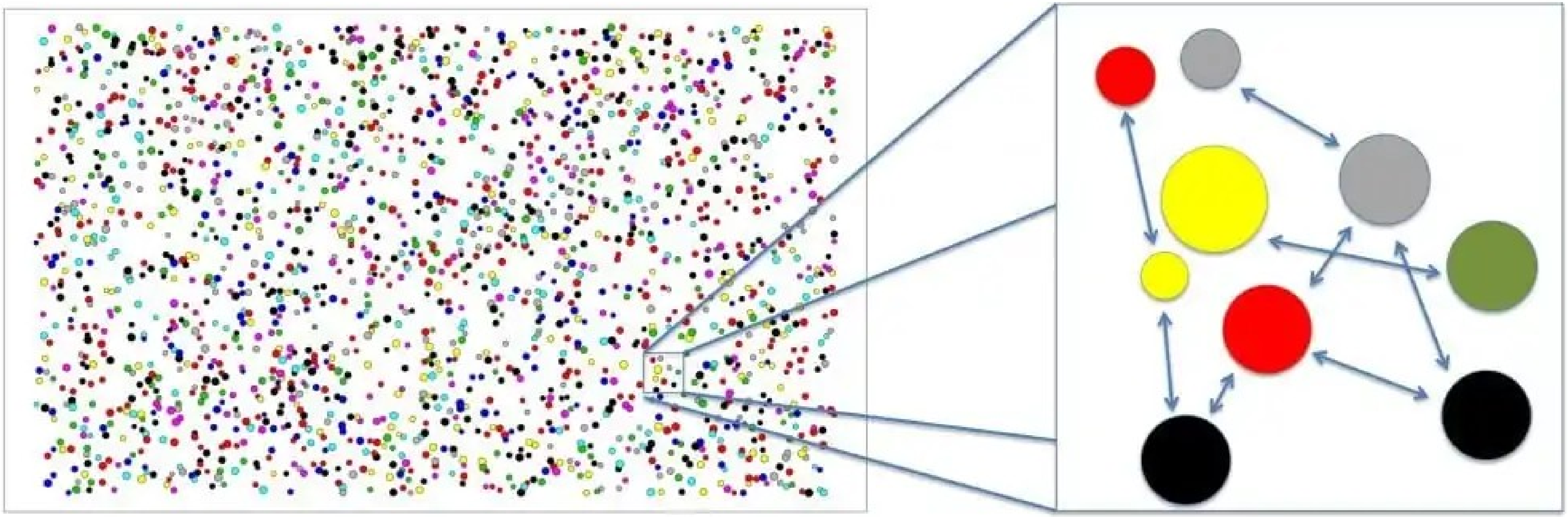
next step: FSDE's

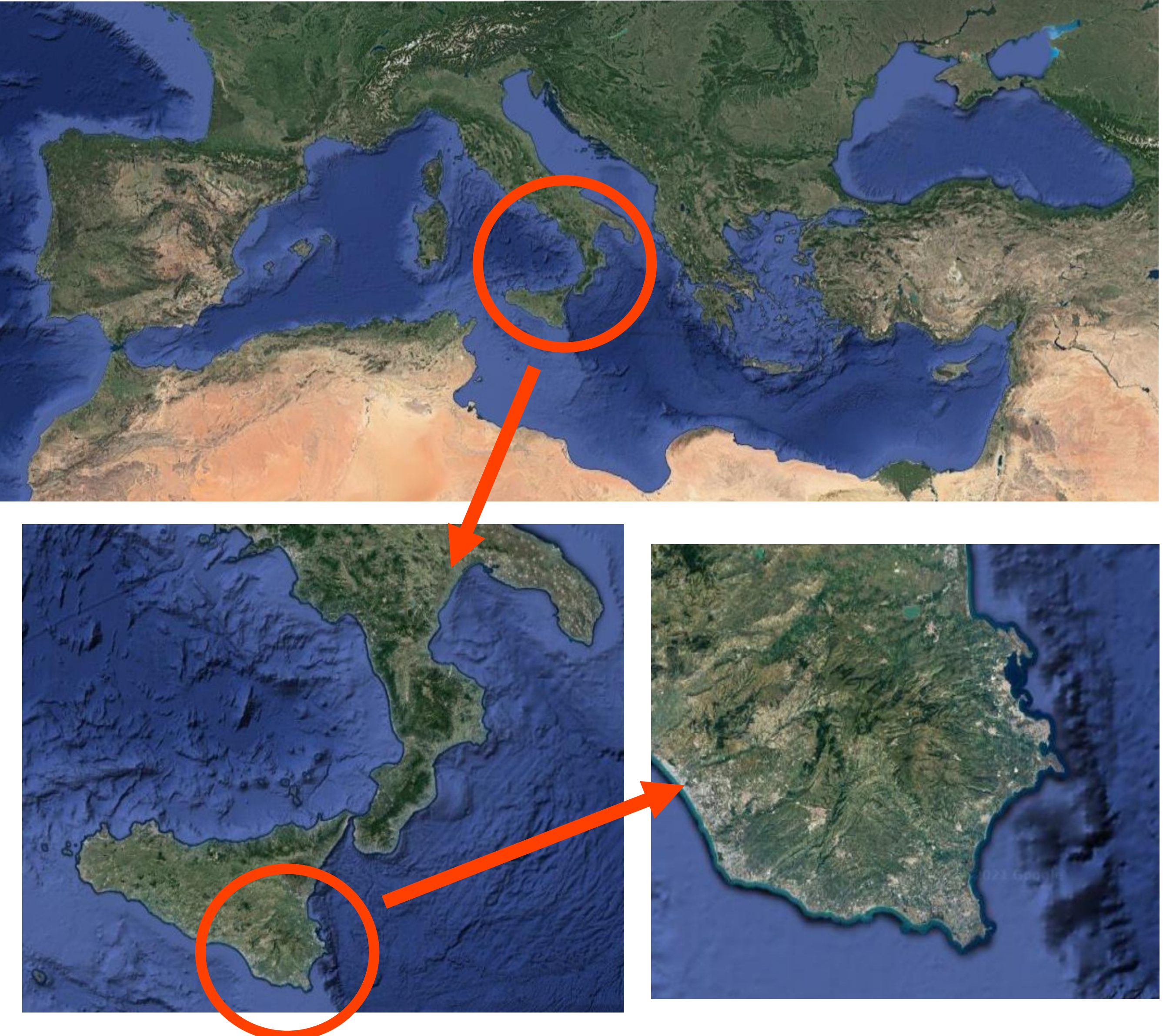
- if we introduce some driving stochastic process (diffusion) in addition to the deterministic derivative (drift), we obtain a FSDE. May drive such FSDE with different noises...

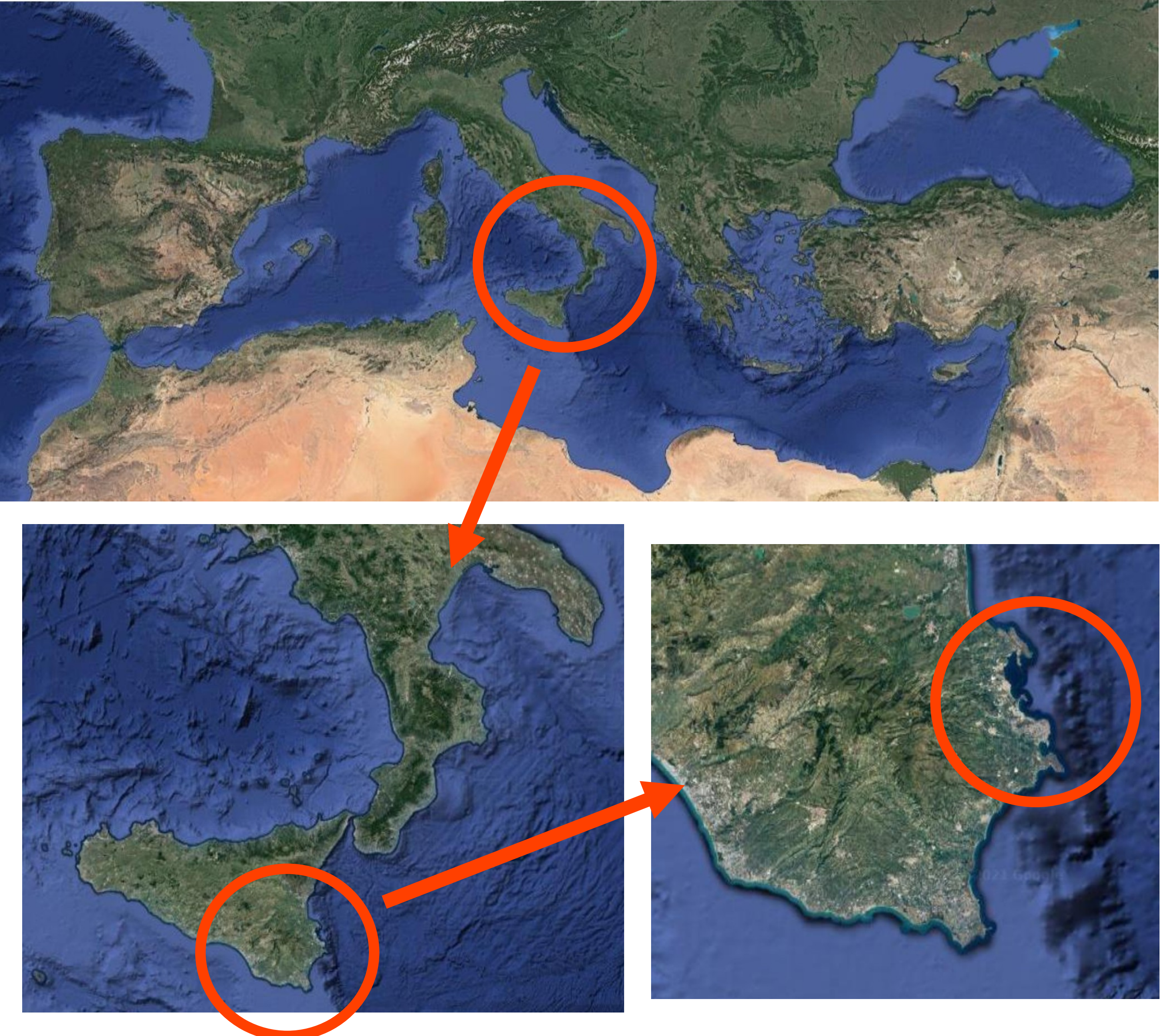
- Notice that by definition (GL) this FSDE is in any case non-local for non-integer α

- The same would happen if adding noise to a delay-differential equation, DSDE.

nonlocal stochastic dynamical systems: ABM's

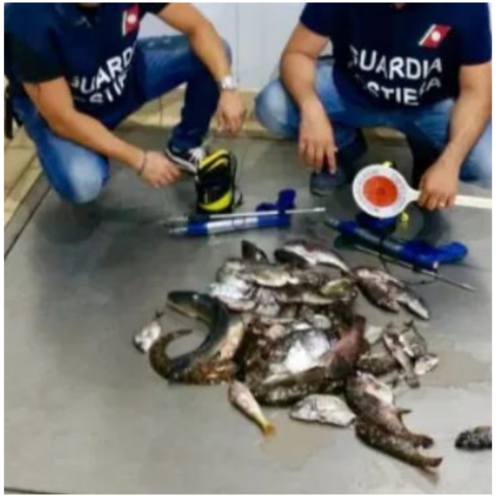




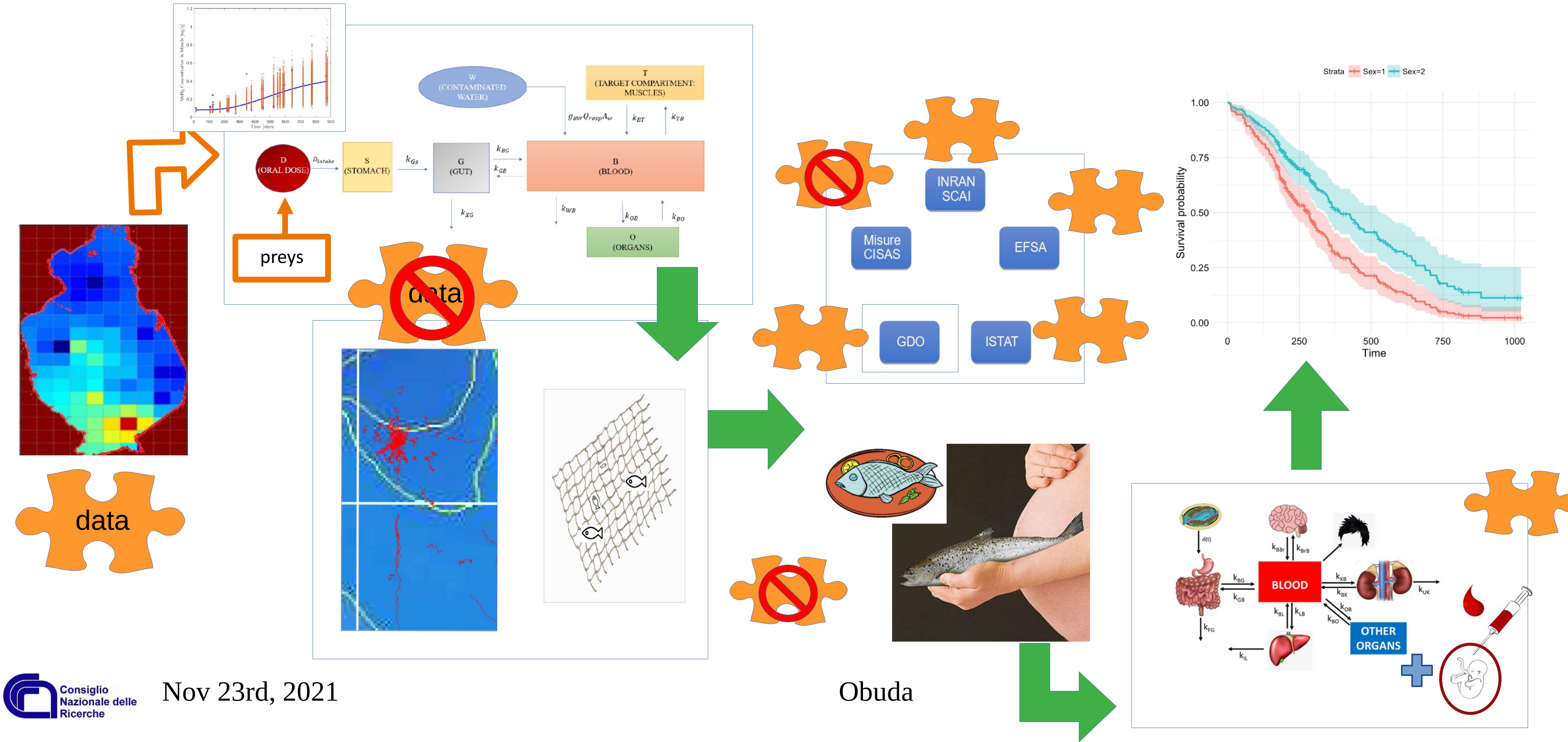


Fishing...

... but!

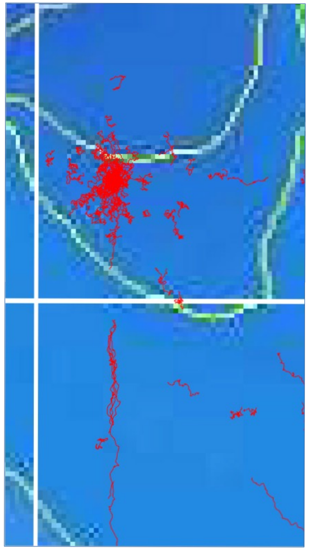


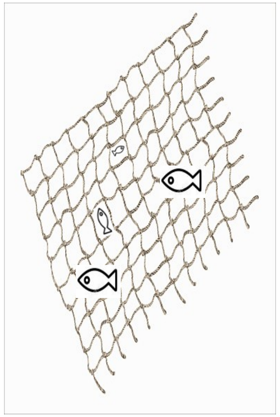
Overall modelling effort



Agent Motion & Fishing Model
(AMoFiM V01.14.02)

$$X(t+1) = X(t) + (1-\alpha)\, D\, Z_1 + \alpha\,(X(t) - X(t-1)) + \beta\, V_{max}(L(t))\, \frac{(X_v(t) - X(t))}{1 + (X_v(t) - X(t))} \quad (1)$$





$$Y(t+1) = Y(t) + (1-\alpha)\, D\, Z_2 + \alpha\,(Y(t) - Y(t-1)) + \beta\, V_{max}(L(t))\, \frac{(Y_v(t) - Y(t))}{1 + (Y_v(t) - Y(t))} \quad (2)$$

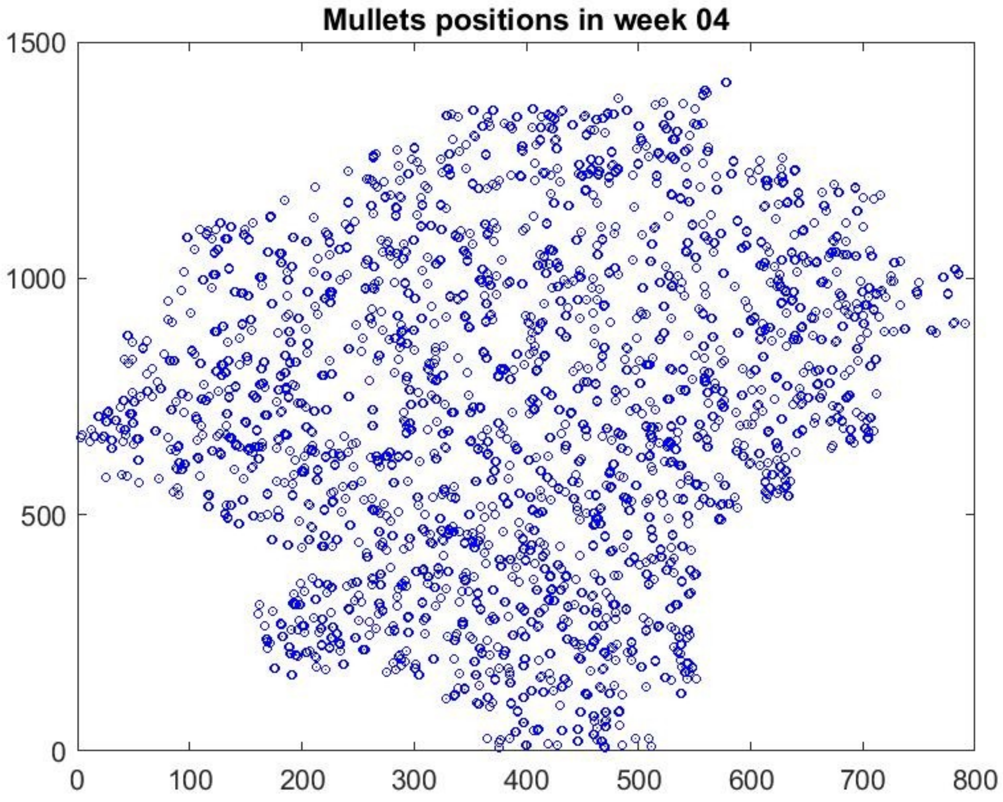
$$Z(t+1) = Z_b(t+1) \quad (3)$$

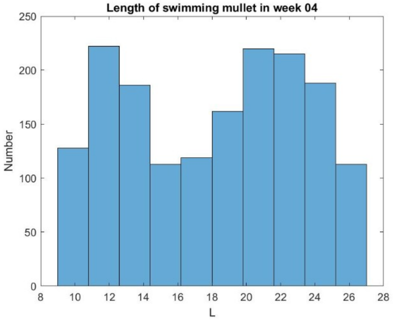
$$L(t+1) = L(t) + k\,(L_{inf} - L(t))\,\Delta t \quad (4)$$

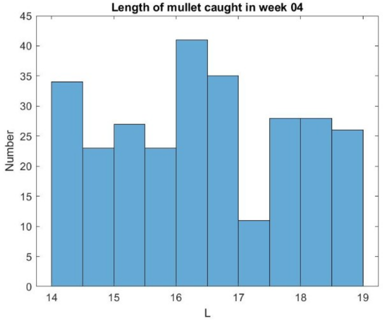
$$W(t+1) = a_{fish}\, L(t+1)^{b_{fish}} \quad (5)$$

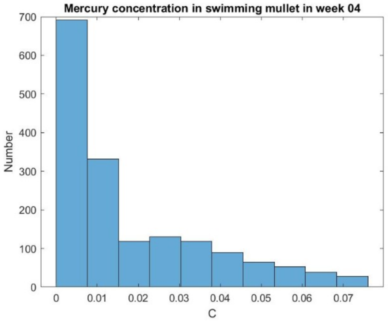
$$V_{max}(L(t)) = \frac{L(t)^{\gamma}}{L_{50}^{\gamma} + L(t)^{\gamma}}$$

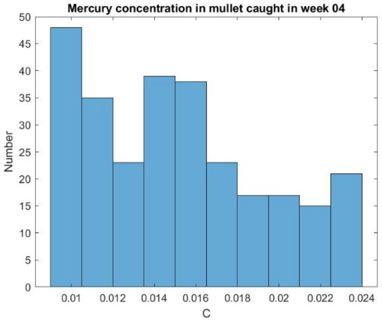
AMoFiM simulation (stochastic)











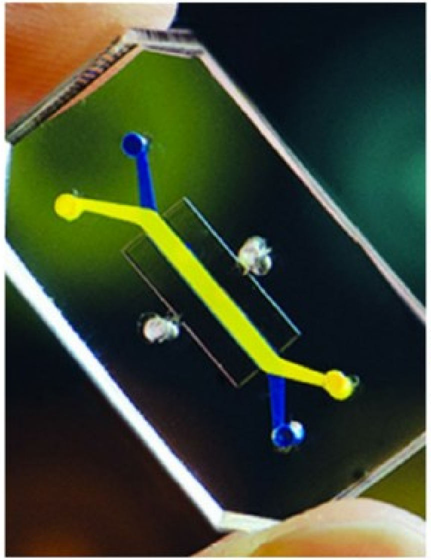
another example

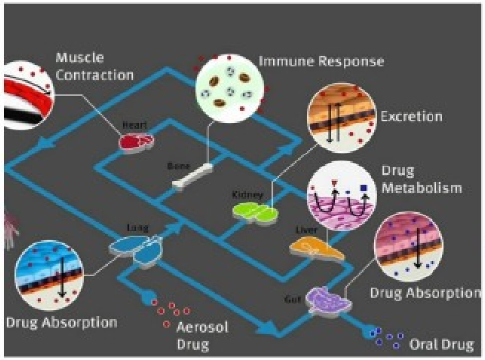
from fish population dynamics

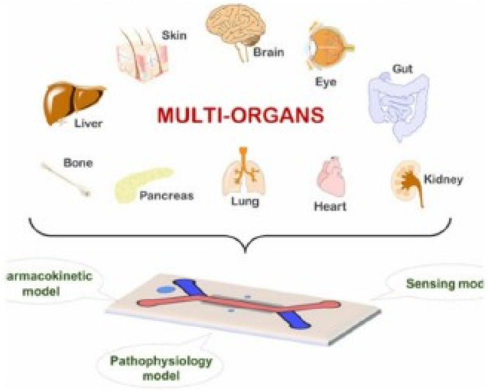
to cancer immunity

Organ On Chip (OOC)

- microfluidic chips
- biological (physiochemical) environment
- recreates in vivo systems in vitro





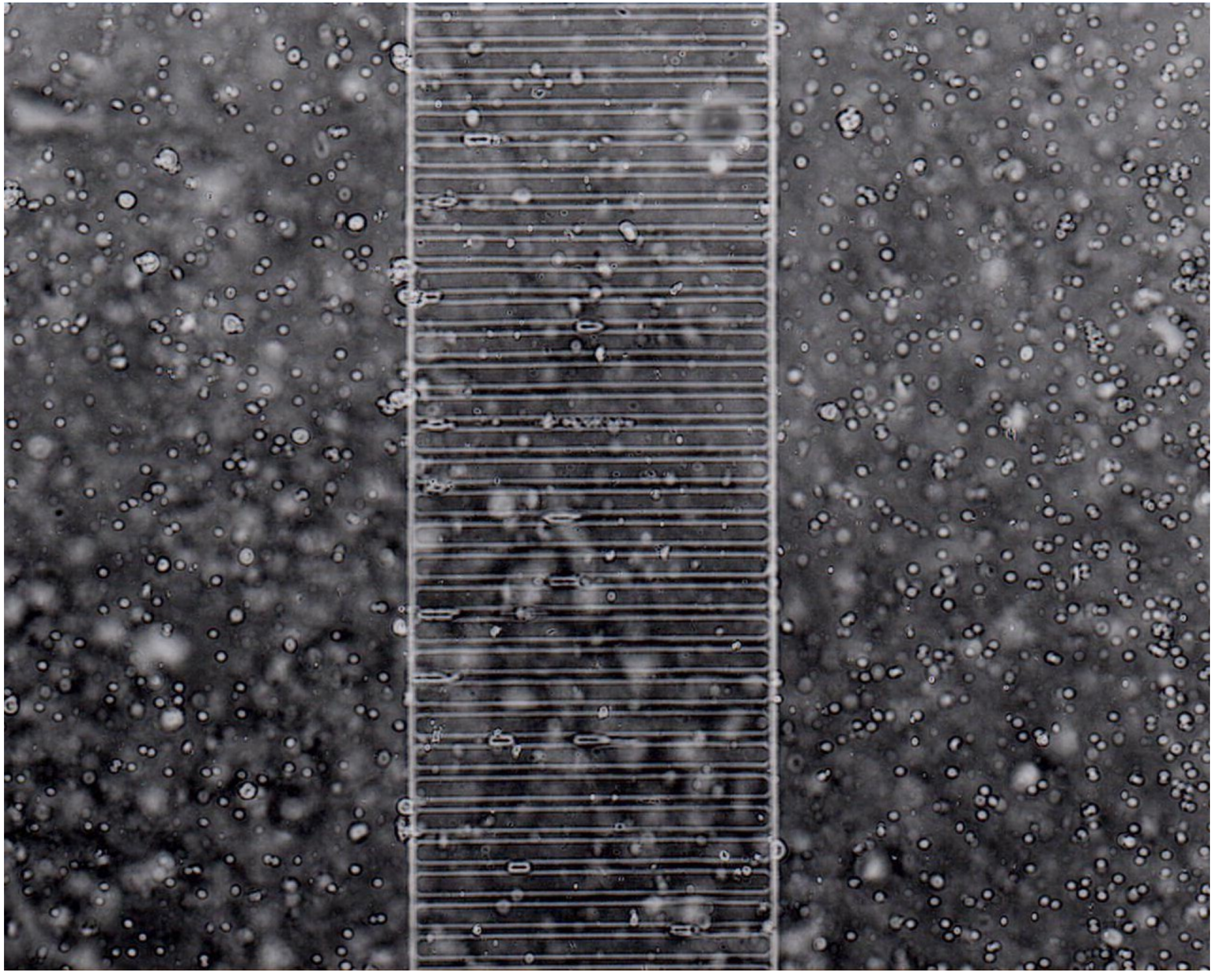


Consiglio Nazionale delle Ricerche

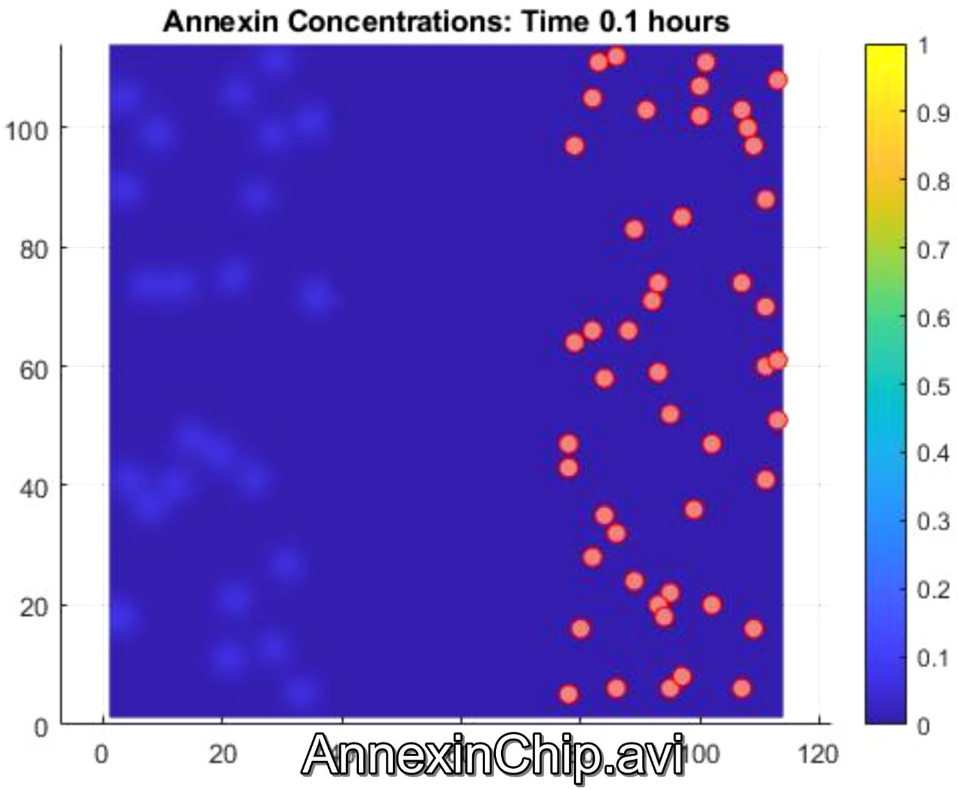
Nov 23rd, 2021

Our preparation

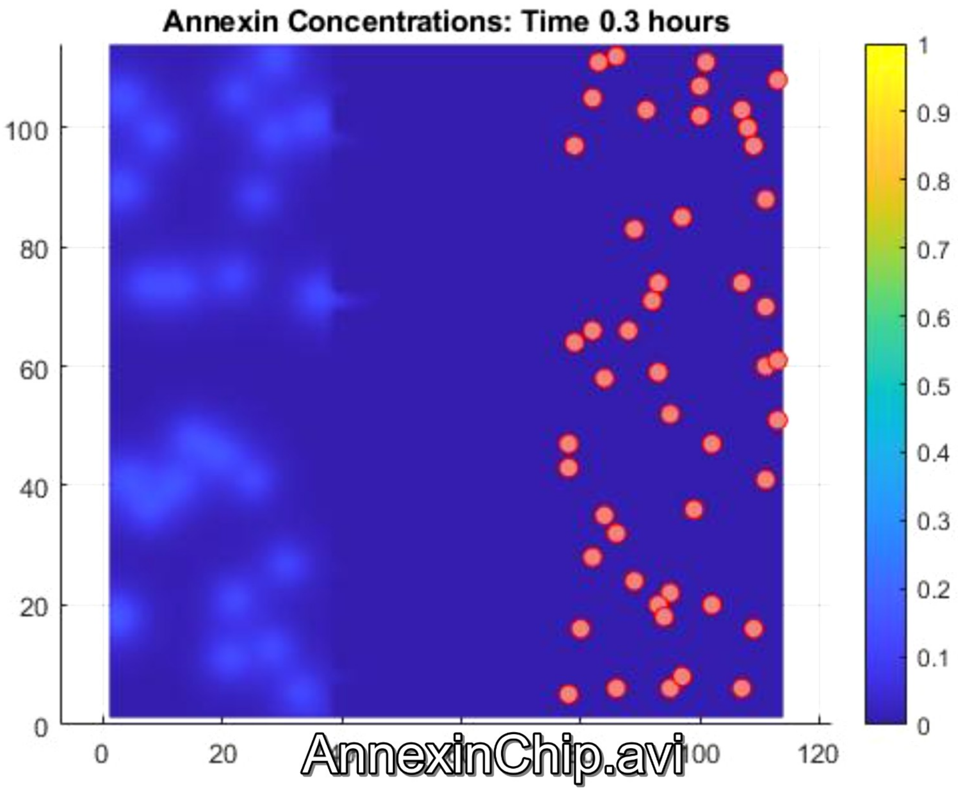
- Treated tumor + leukocytes MCA205-WT
- Videos recording positions of cells (1 frame q 2 min.)
- Goal: visualize treatment effect on migration rate, aggregation, inhibition of cancer cell proliferation



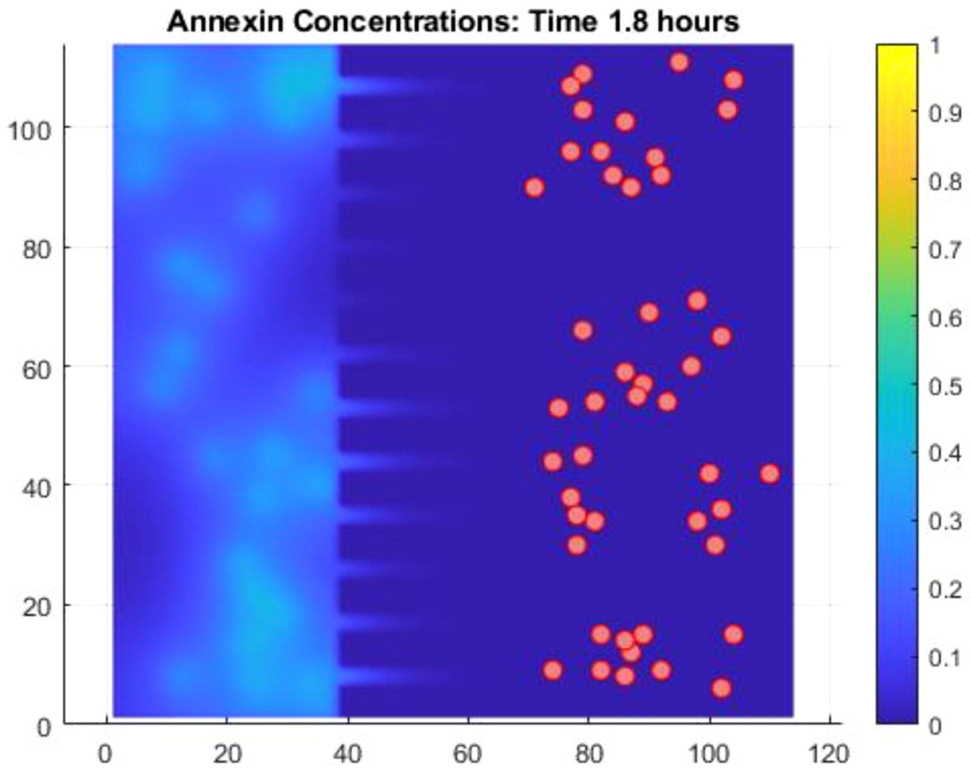
Migration Model



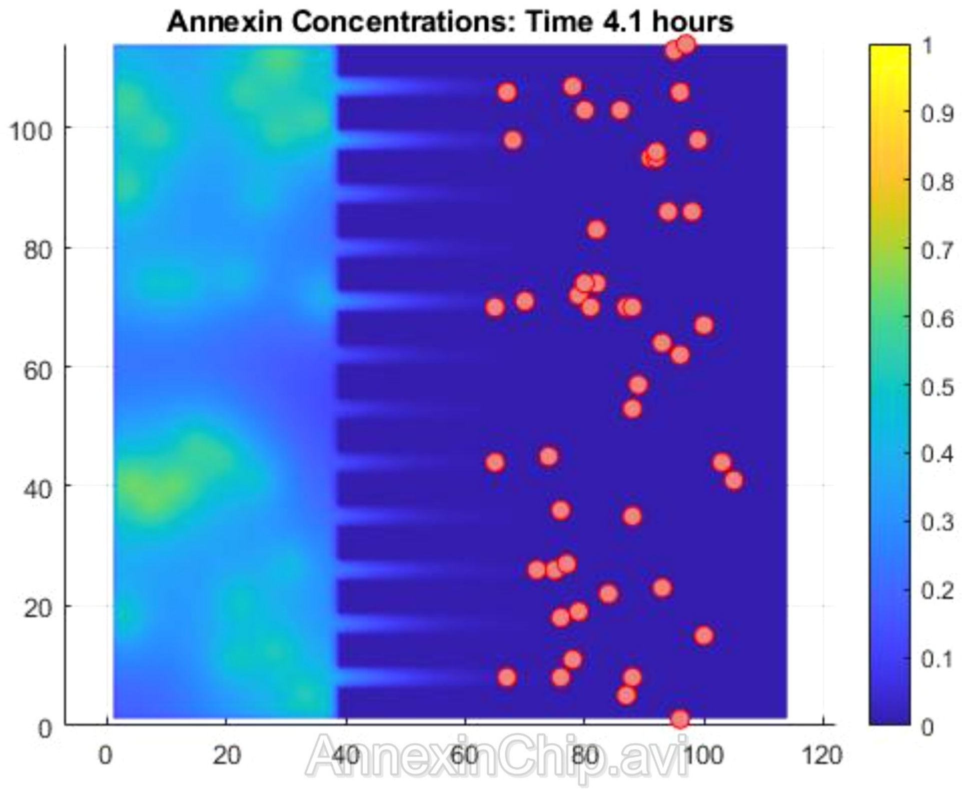
Migration Model



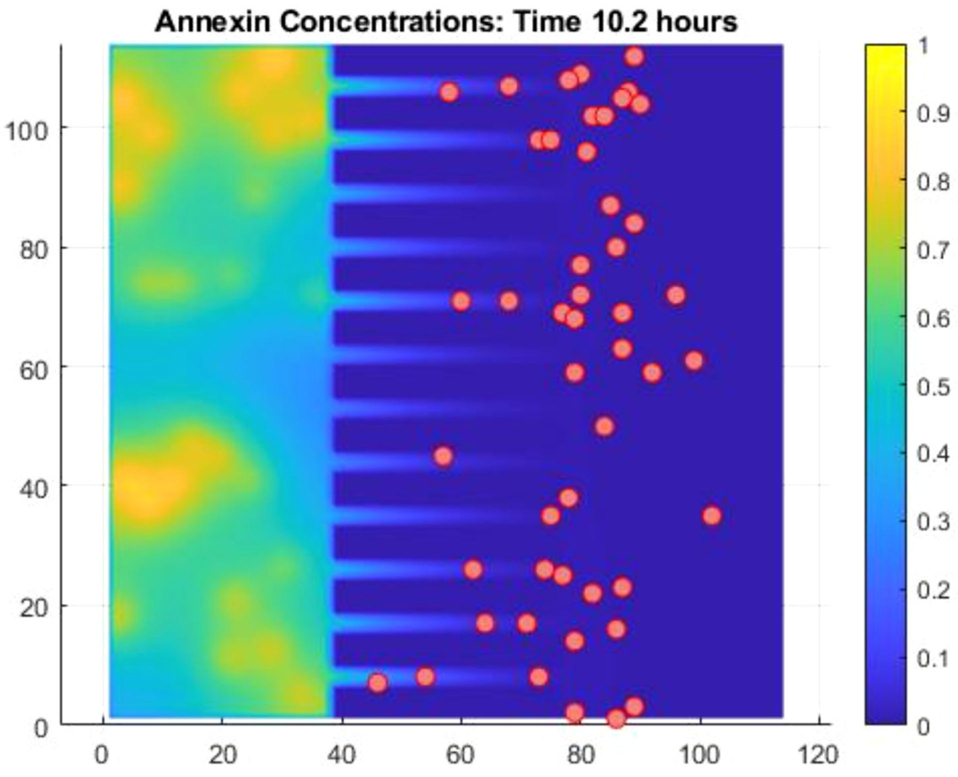
Migration Model



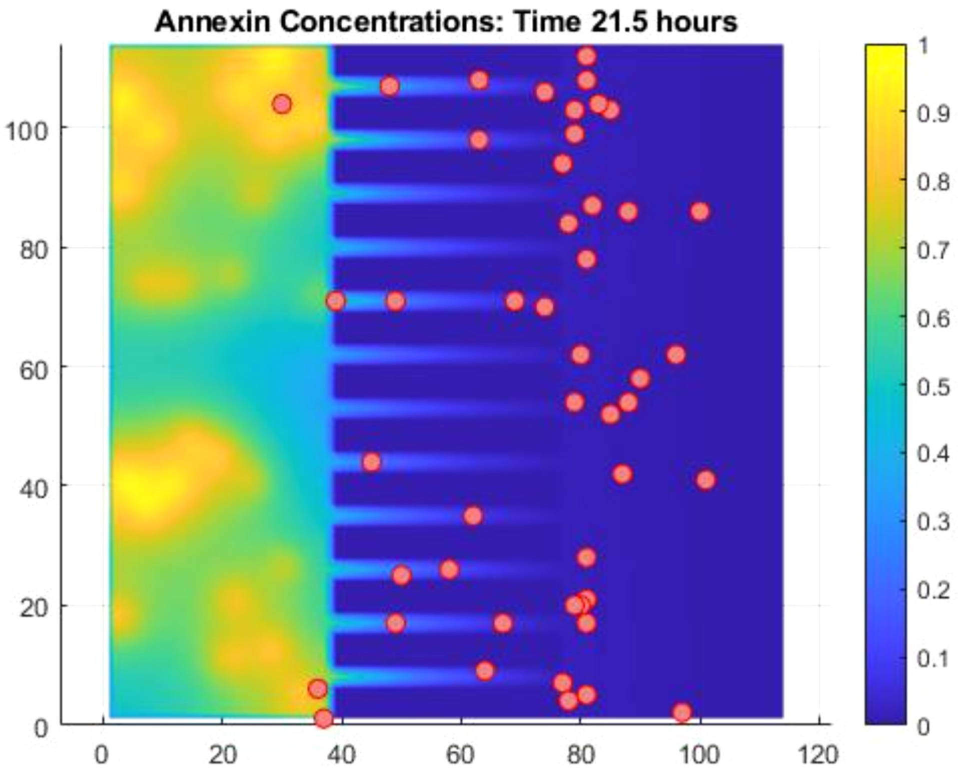
Migration Model



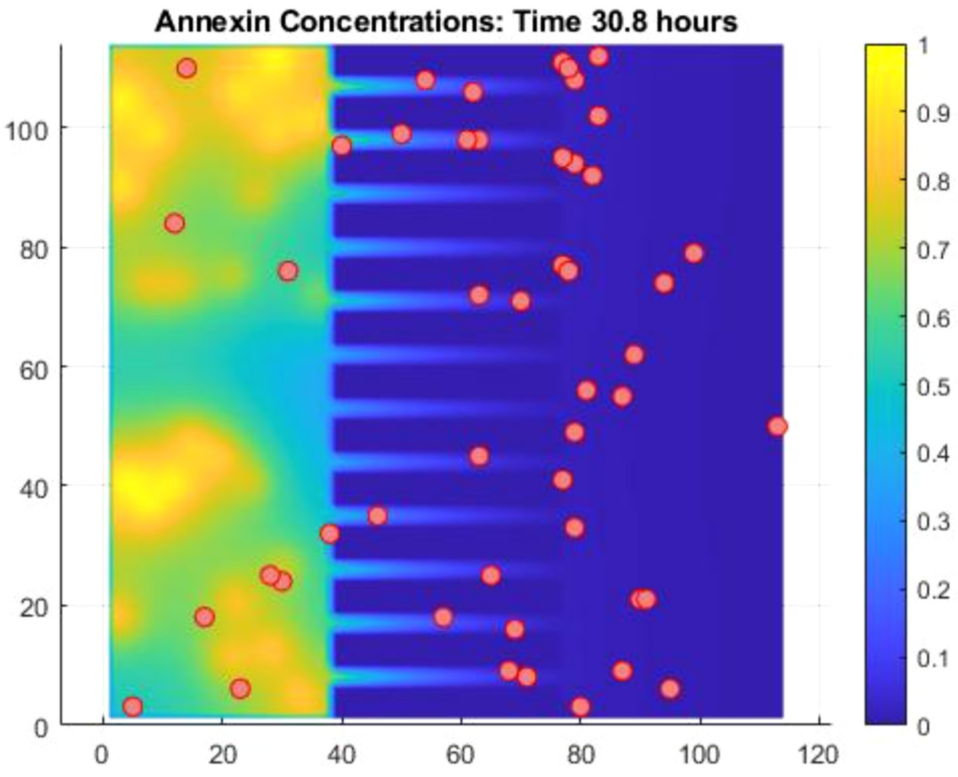
Migration Model



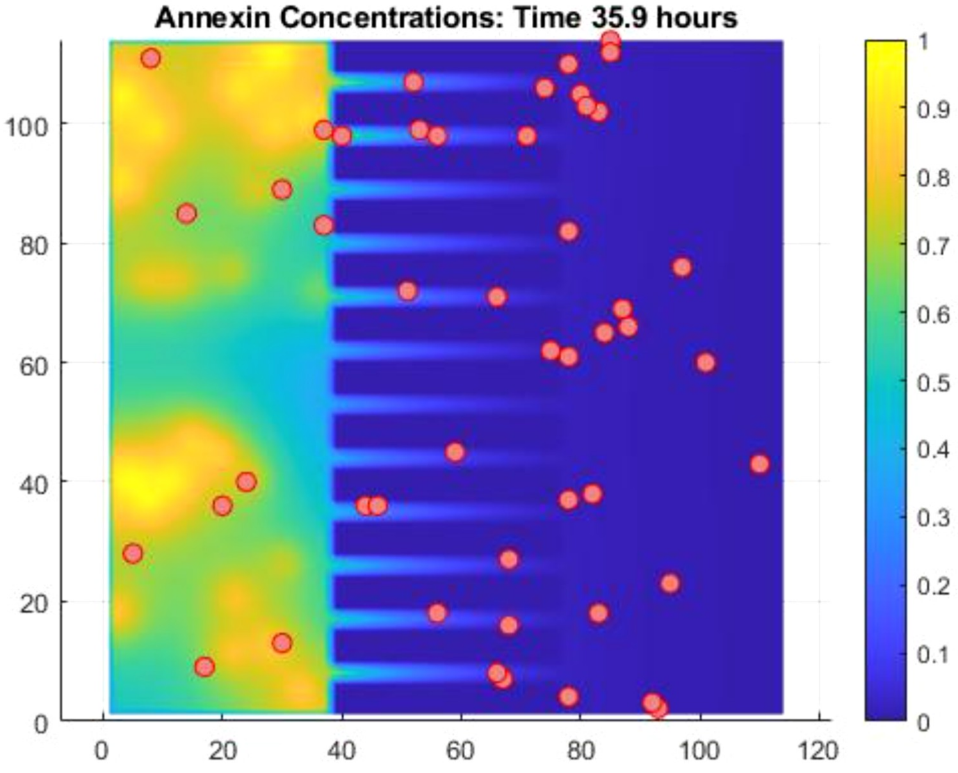
Migration Model



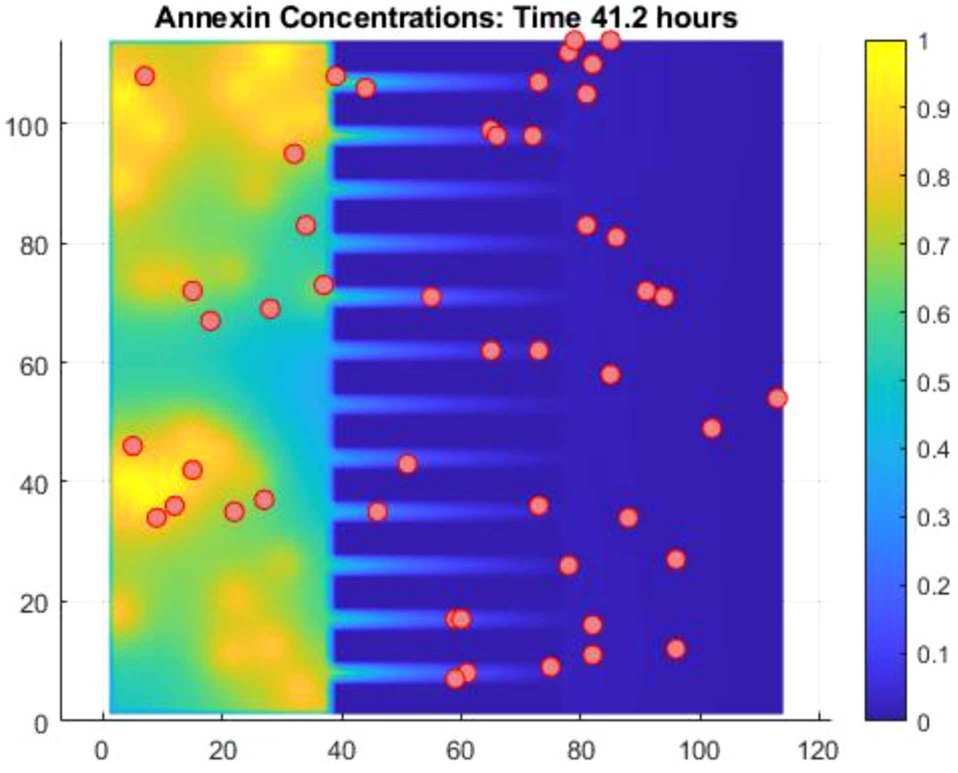
Migration Model



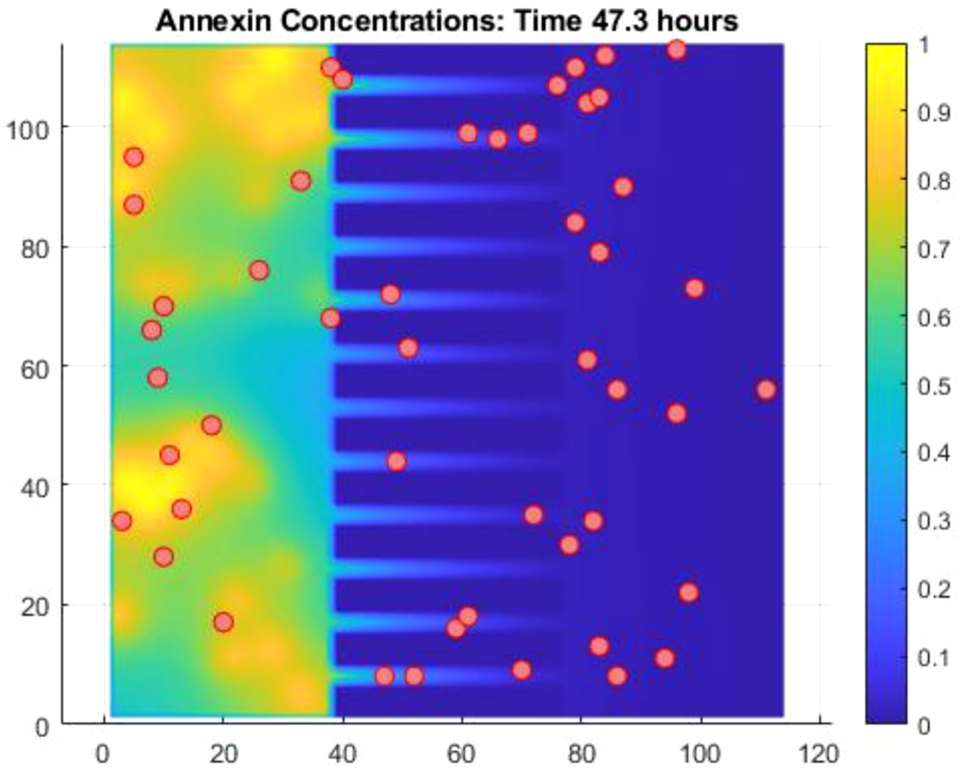
Migration Model



Migration Model



Migration Model

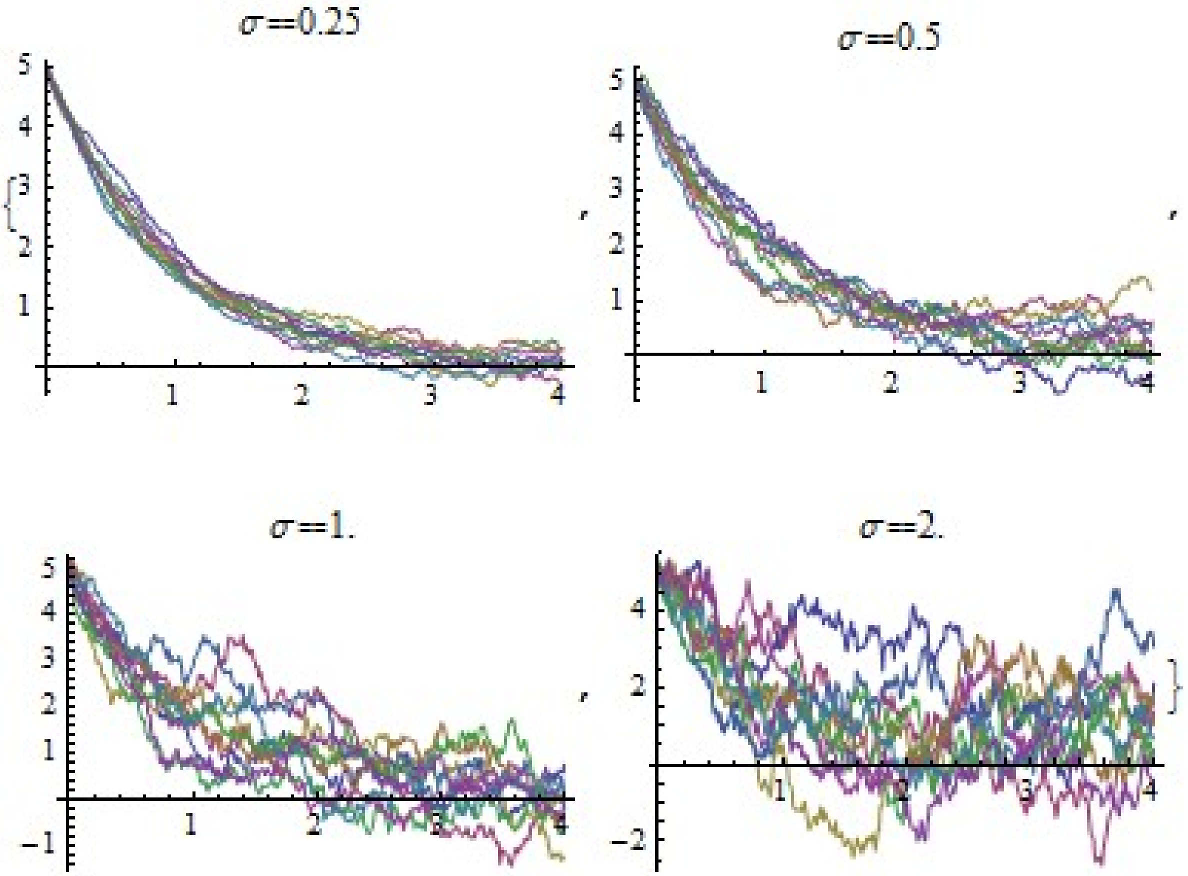


so, now that we have stochastic models...

the question is:

how to estimate the model parameters?

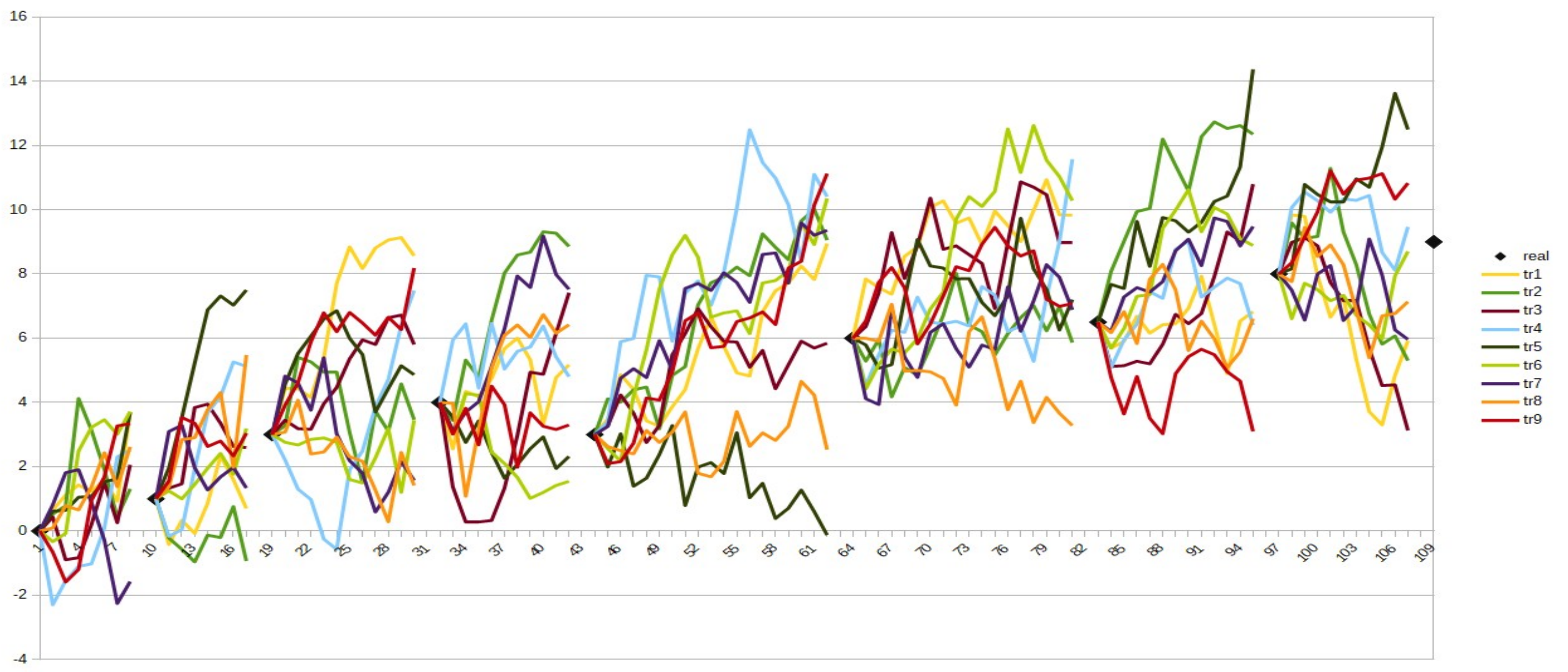
SDE's: ALL trajectories SAME drift parameters



ML Estimation

- easy case: Y observed is Markovian
  - implies NO hidden variables and NO observation error
- Hard but doable if hidden process is markovian

Markovian Y



16
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12
10
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-2
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106
109
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tr4
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tr7
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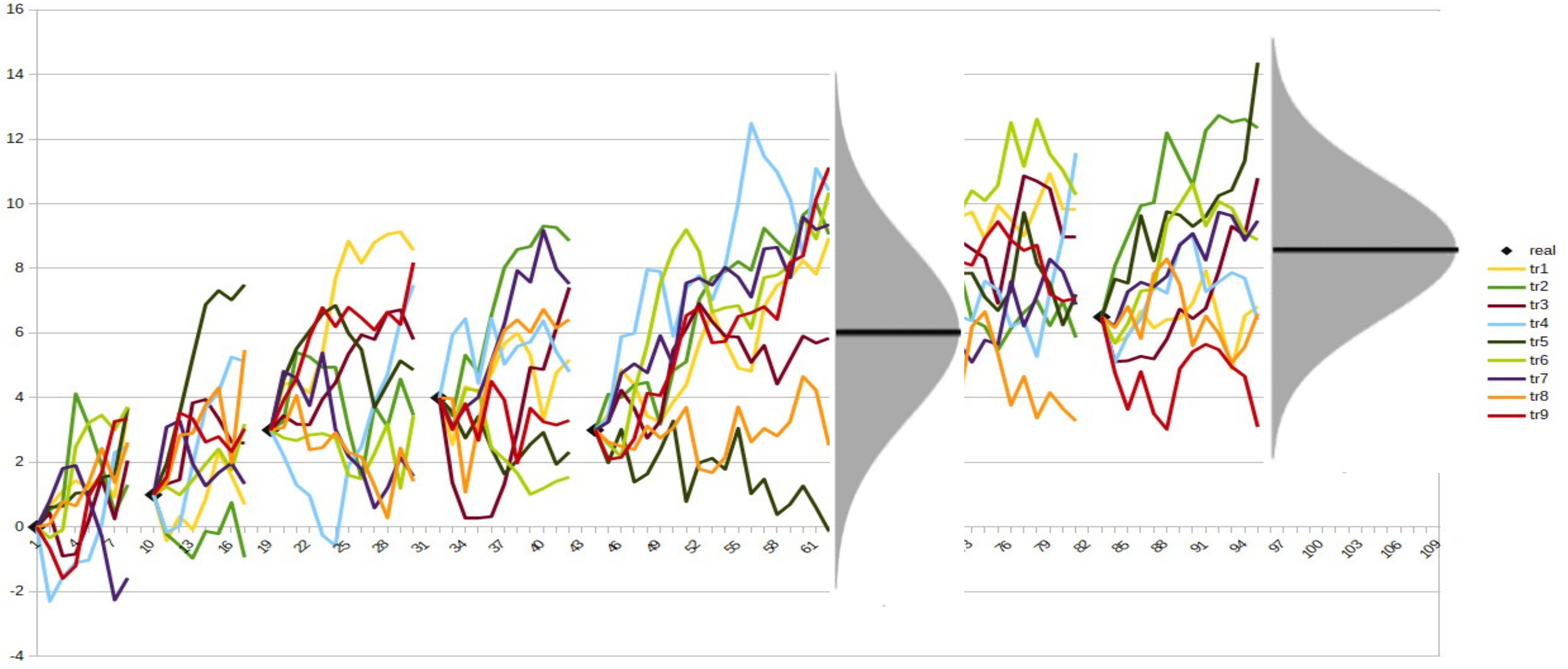
Markovian Y



Nonlocal dynamical models: direct MLE

- Generate many trajectories over whole timeframe
- compute density at each observation
- assume independent observations and multiply
- OPTIMIZE!

local vs. nonlocal stochastic models

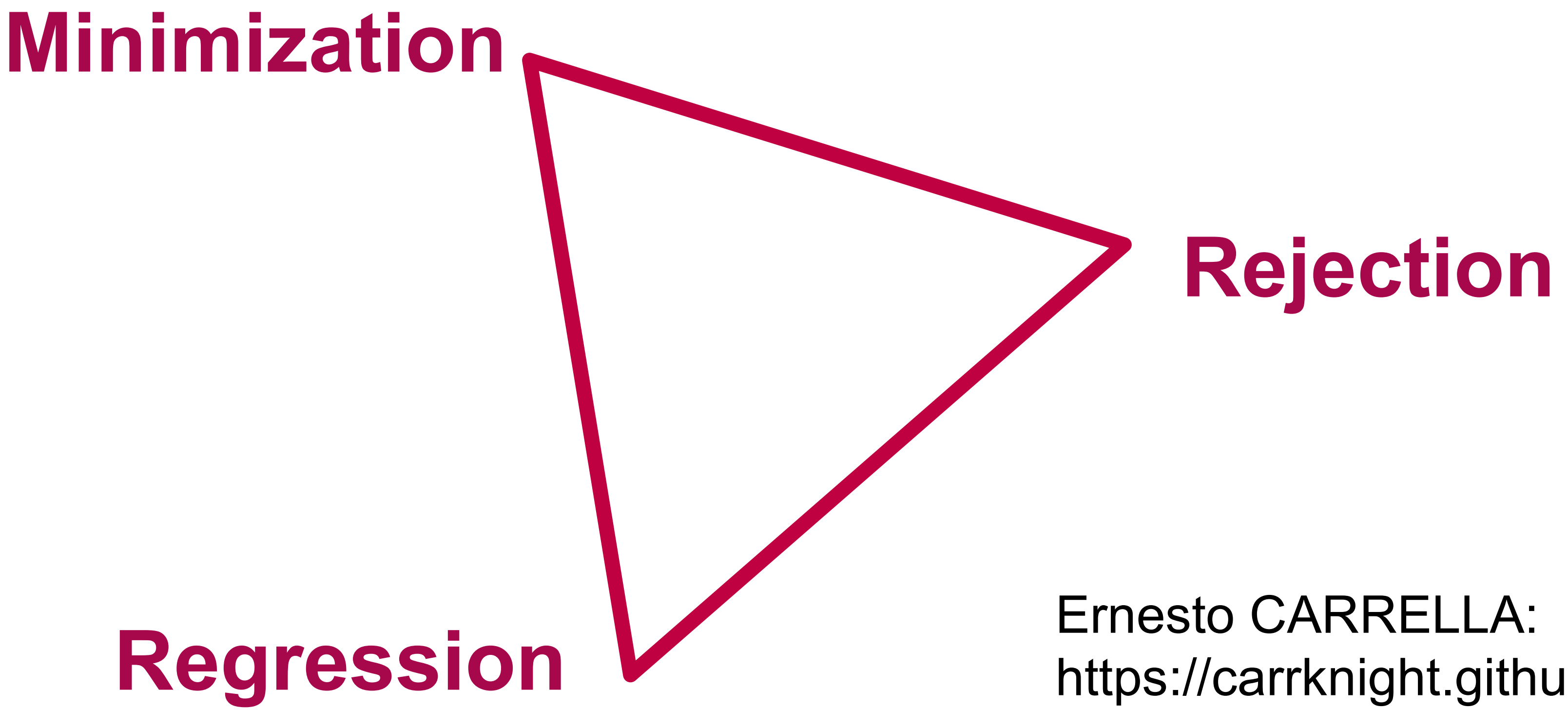
- SDEs may be nonlocal if underlying process non-markovian (FSDE, DSDE by definition)
- ABMs nonlocal if incompletely observed (e.g. only position, not inner state)

Nonlocal dynamical models: direct MLE

- ~~Generate many trajectories over whole timeframe~~
- ~~compute density at each observation~~
- ~~assume independent observations and multiply~~
- OPTIMIZE!

cannot do!

Estimating nonlocal stochastic models

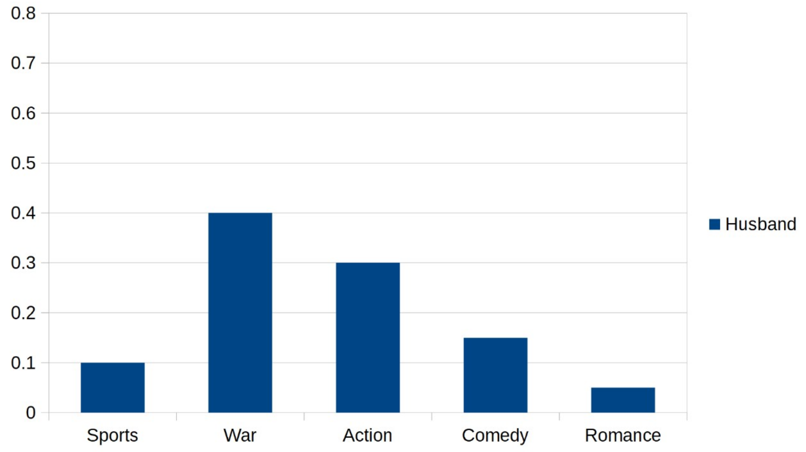


Ernesto CARRELLA:
https://carrknight.github.io/abm/2020/09/22/estimation.html

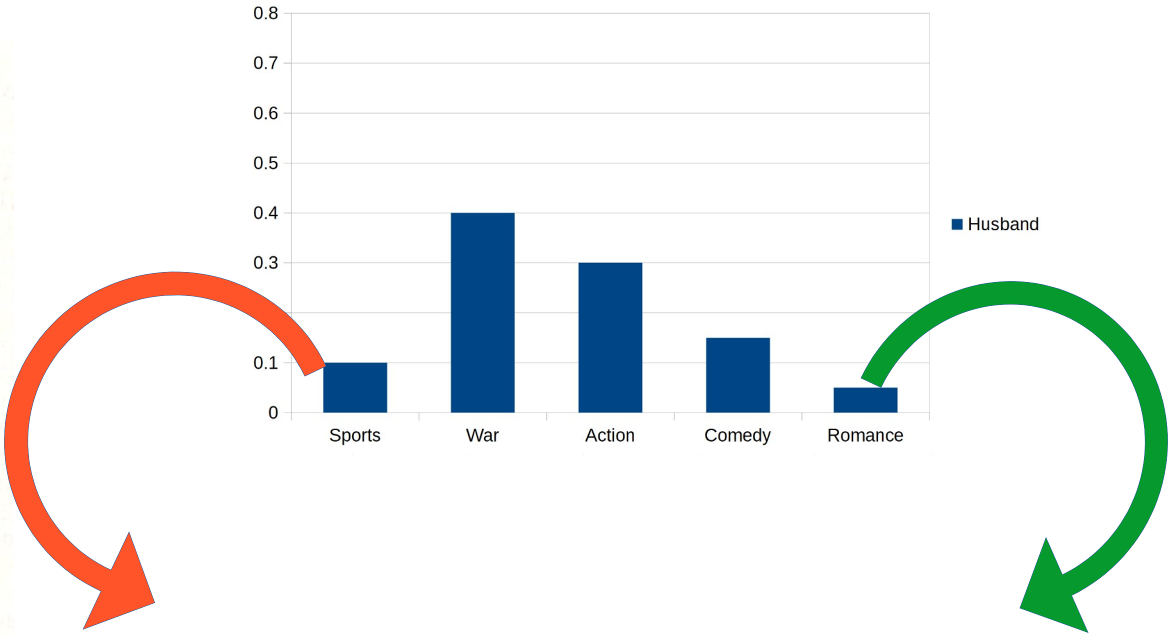
Rejection methods: what's the point?

- MLE means find q such that $P(Y^o|\theta)$ max.
- Cannot do it? OK, next best thing is...
- ... find (correctly) a (large) sample of θ that are consistent with Y^o, ie. such that $s(Y|\theta)$ near $s(Y^o)$, then use the empirical distribution of this sample to infer anything you want on θ

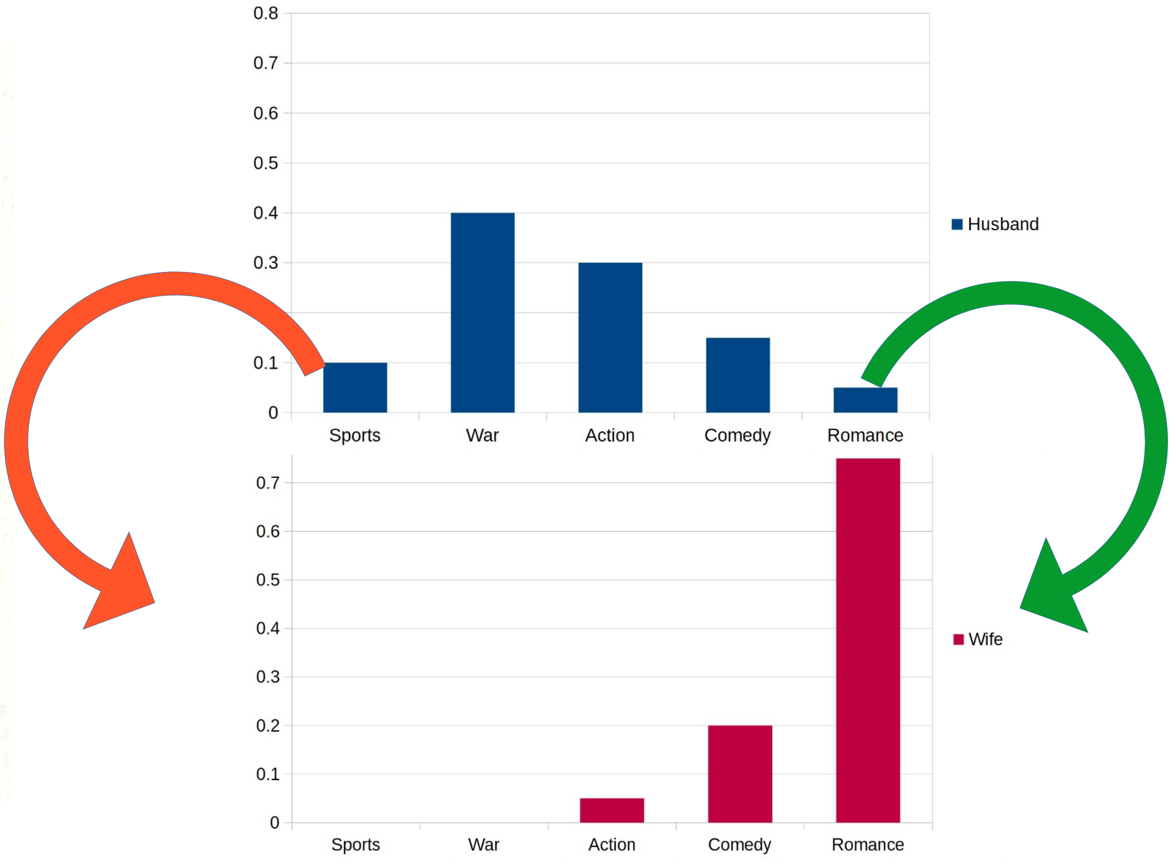
Rejection sampling


0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Sports
War
Action
Comedy
Romance
Husband

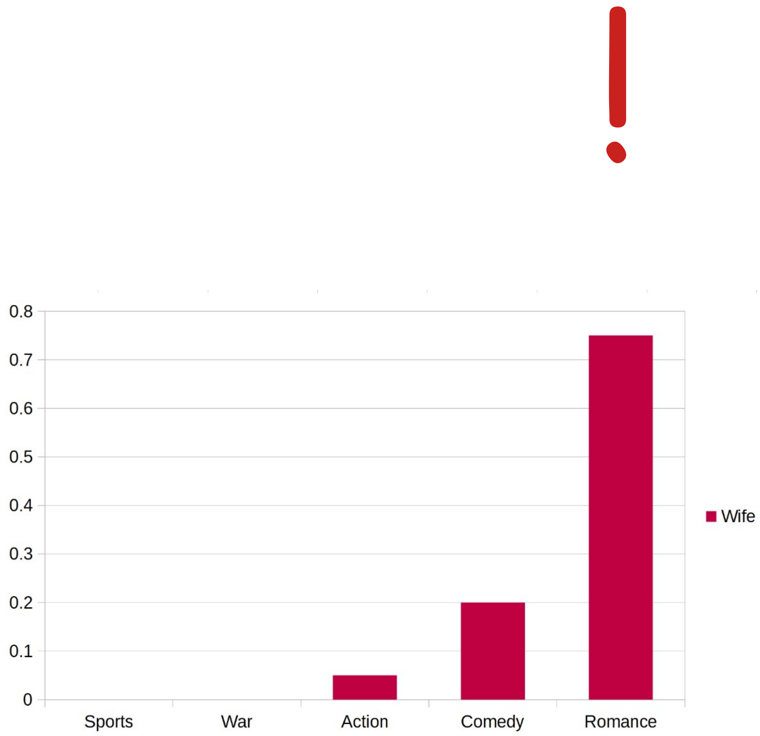
Rejection sampling



Rejection sampling



Rejection sampling



Approximate Bayesian Computing

easiest algorithm

(there are more sophisticated ones)

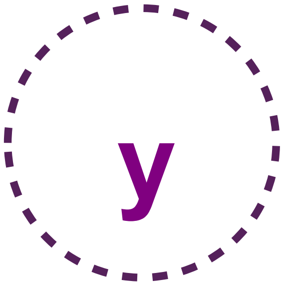
Approximate Bayesian Computing

$\mathbf{y}$

We start with having OBSERVED some (vector) $\mathbf{y}$, which we assume is being generated by some model depending stochastically on unknown (vector) parameter θ

$$\mathbf{y} = \mathbf{y}(\theta)$$

Approximate Bayesian Computing



$f(\theta)$

Since we do not know the distribution $g(\theta)$ of θ, we wish to approximate it with the empirical distribution of a sample of GOOD θ_i's.

We begin with an <u>appropriate</u> **proposal distribution** $f(\theta)$

Approximate Bayesian Computing

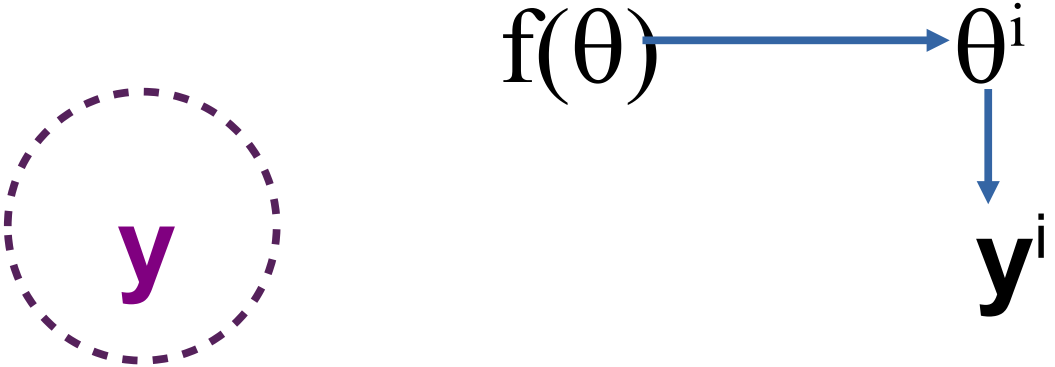
$f(\theta) \longrightarrow \theta^i$

y

we can generate θ_i's. from $f(\theta)$

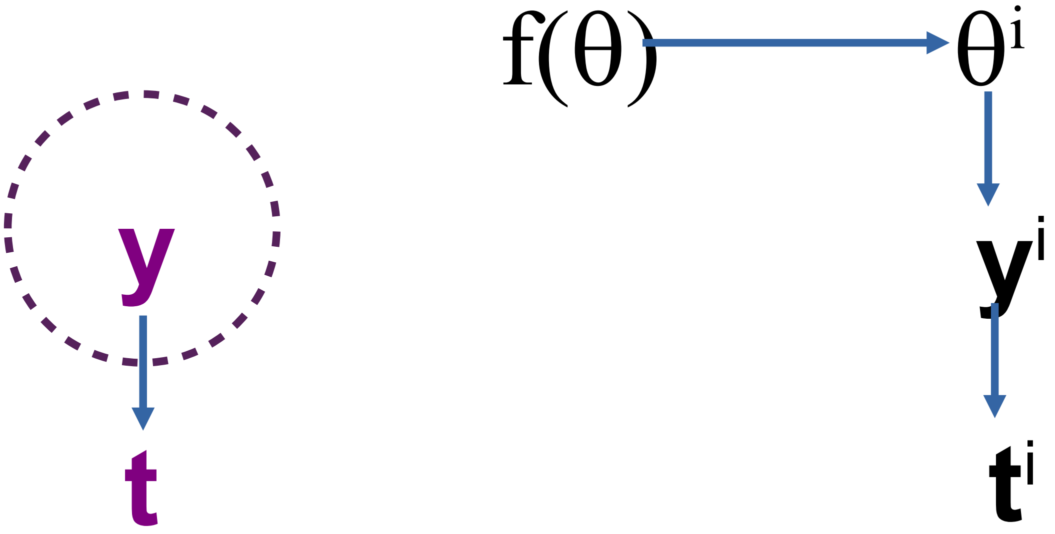
but... how GOOD are they?

Approximate Bayesian Computing



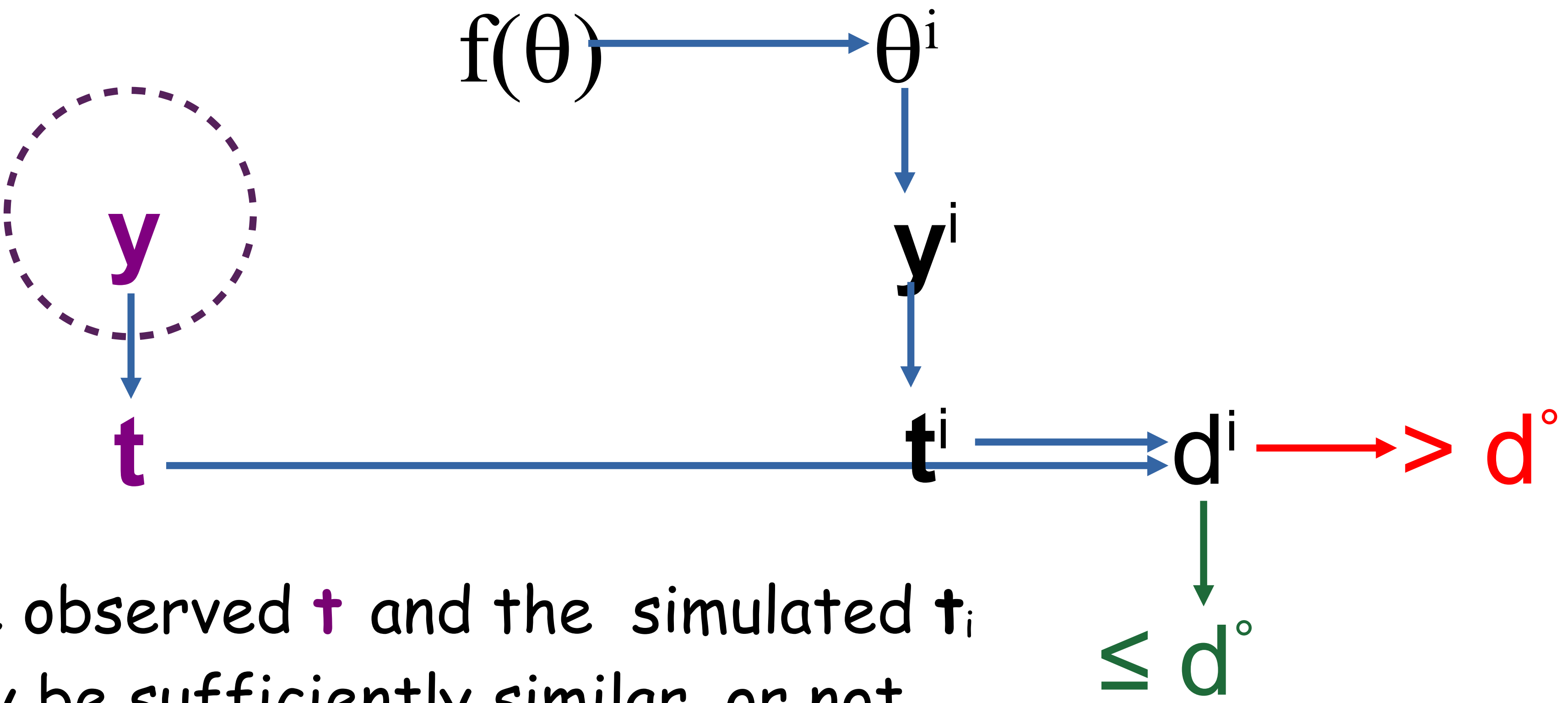
using each θ_i we can generate a whole (virtual) sample $\mathbf{y}_i$

Approximate Bayesian Computing



and can compute an <u>appropriate</u> statistics **t** from both the observed data **y** and from the simulated data **y**$_i$

Approximate Bayesian Computing



the observed t and the simulated t_i
may be sufficiently similar, or not

Approximate Bayesian Computing

$$f(\theta) \longrightarrow \theta^i \longrightarrow y^i \longrightarrow t^i$$

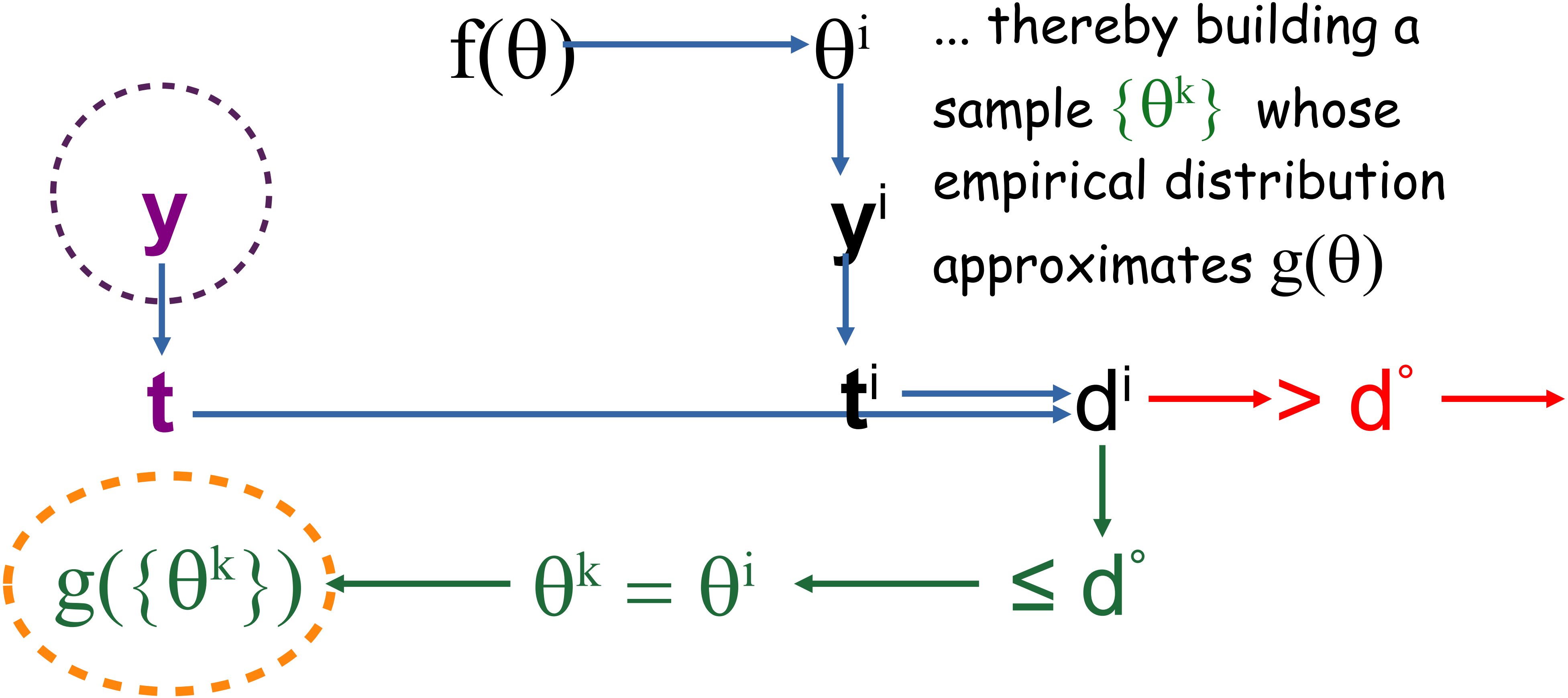
$$y \longrightarrow t$$

$$t,\ t^i \longrightarrow d^i \longrightarrow\ > d^{\circ} \longrightarrow$$

$$d^i \longrightarrow\ \leq d^{\circ} \longrightarrow \theta^k = \theta^i$$

if **t** and **t_i** are similar we **accept** the candidate θ_i as the k-th new sampled θ, else we **reject** it…

Approximate Bayesian Computing



... thereby building a sample $\{\theta^k\}$ whose empirical distribution approximates $g(\theta)$

but... not so good!

- Rejection/ABC:
  - still sensitive to choice of statistics
  - high computational cost

next goals:

- Obtain relevant, appropriate statistics from the observed dynamics of the biological situations

- Devise a formally correct, numerically effective method for parameter estimation of nonlocal stochastic models

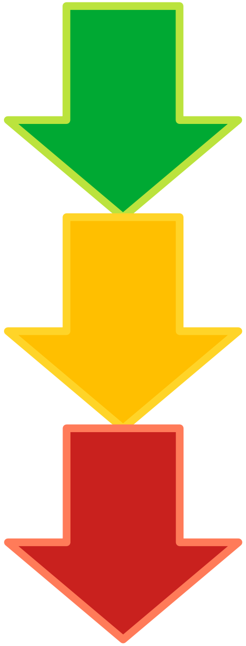
conclusion: M, E & C

modeling, estimation and control

idea

research

application



modeling, estimation and control

- Addressing biological problems prompts methodological advances
- Teamwork: numerics, analysis, statistics, physiology, optimization
- M, E & C: an eternal golden braid.

Thank you!

Óbudai Egyetem
Pro Scientia et Futuro

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NATIONAL RESEARCH COUNCIL (CNR)

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