QR and Medical Applications

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Outline

1. Introduction
2. A modeling framework for pathophysiological systems
3. Model-based systems for medical tasks
    - Diagnosis
    - Therapy Planning
    - Monitoring
4. New challenging applications of QR to the medical/biological domain

Introduction

The need for models in the medical domain for:

- understanding patho-physiological mechanisms
- predicting, simulating, controlling patho-physiological behaviors
- interpreting data streams

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Compartmental Modeling

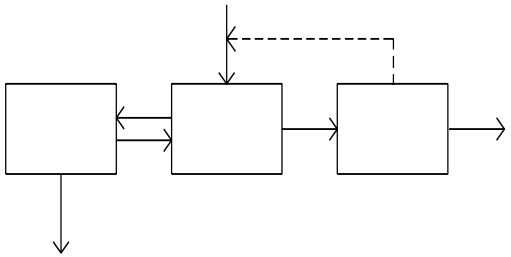
Well-known modeling technique for the representation of the behavior of complex systems. It can be properly exploited for the formal description of the dynamics of chemical reactions and material transfer processes.

Main application domains:

- biology
- medicine
- epidemiology
- ecology
- hydrology
- chemical engineering

Model: representation of the *structure* and *behavior* of a system.

- *structure*: finite set of compartments interacting by exchanging or transforming material.



- *behavior*: set of Ordinary Differential Equations based on the mass balance law. (*Assumption:* the substance is homogeneously distributed)

$$\dot{x}_i = f_{i0} + \sum_{\substack{j=1 \\ j \neq i}}^{n} f_{ij}(x_j) - \sum_{\substack{j=1 \\ j \neq i}}^{n} f_{ji}(x_i) - f_{0i}(x_i) \qquad (1)$$

$$f_{ij} = f_{ij}(x_j; x_l, x_m, ...) \text{ when controlled} \qquad (2)$$

Tools: SAAM - quantitative formulation
QCMF - qualitative formulation

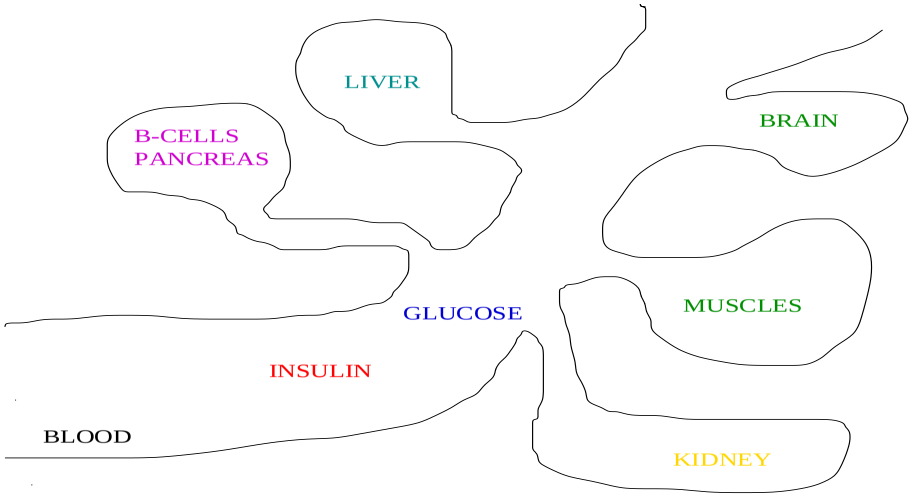
Problems

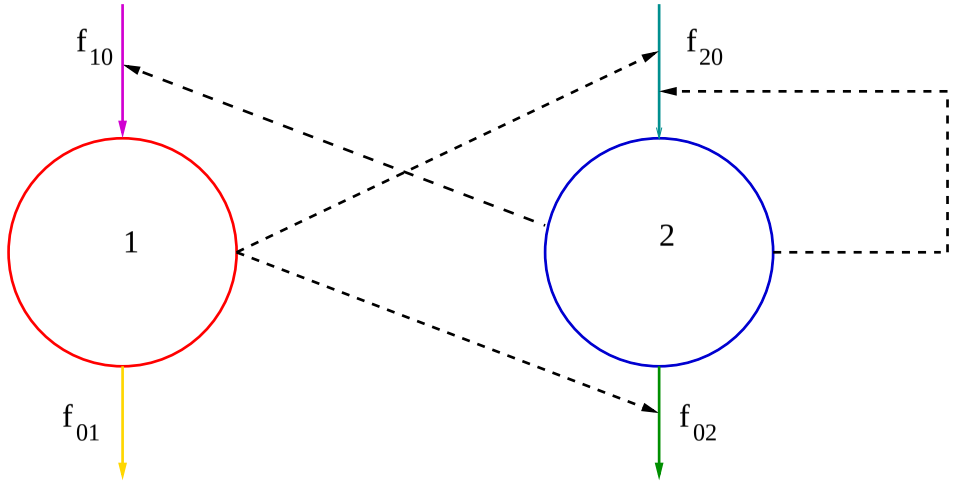
1. Mostly, f_{ij} are *nonlinear* and *unknown*
2. f_{ij} may be reasonably assumed *linear* when the observed dynamics is obtained in response to a *small-signal perturbation* around the system steady-state condition (tracer experiments)
3. the experimental data sets are often *poor* in number and quality, and then identifiability may be hampered also in the linear case

QR may help to find valid alternative solutions

to optimally perform a medical task

Example: Glucose-Insulin control system





$$\dot{x}_1 = f_{10}(x_2) - f_{01}(x_1)$$
$$\dot{x}_2 = f_{20}(x_1, x_2) - f_{02}(x_1, x_2)$$

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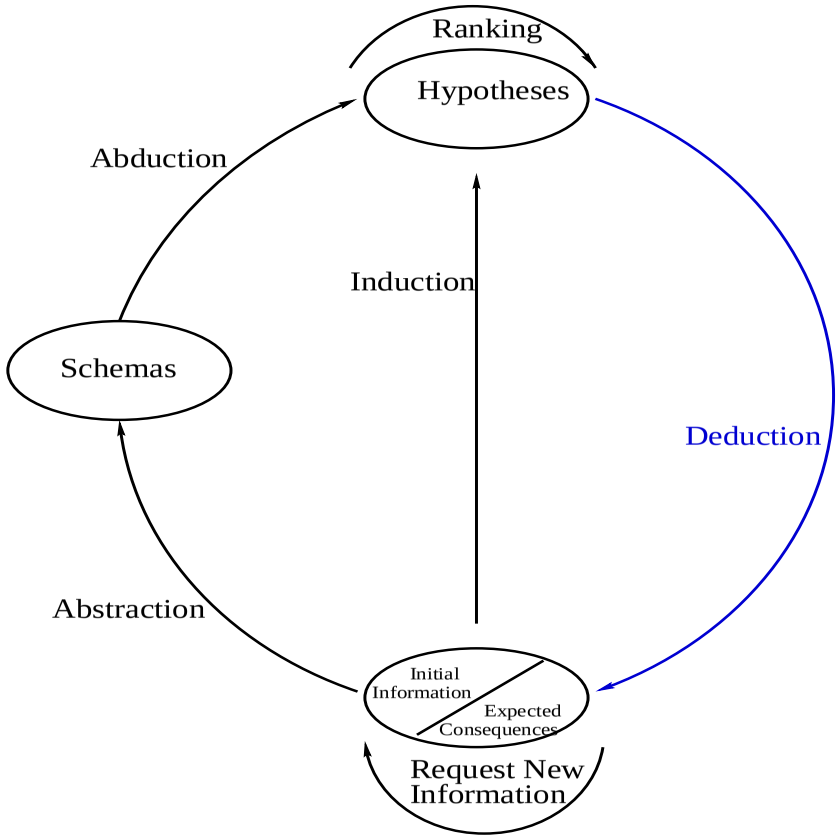
Fundamental tasks in Medical Reasoning

- Diagnosis
- Therapy Planning
- Monitoring

Which level of model representation versus tasks ?

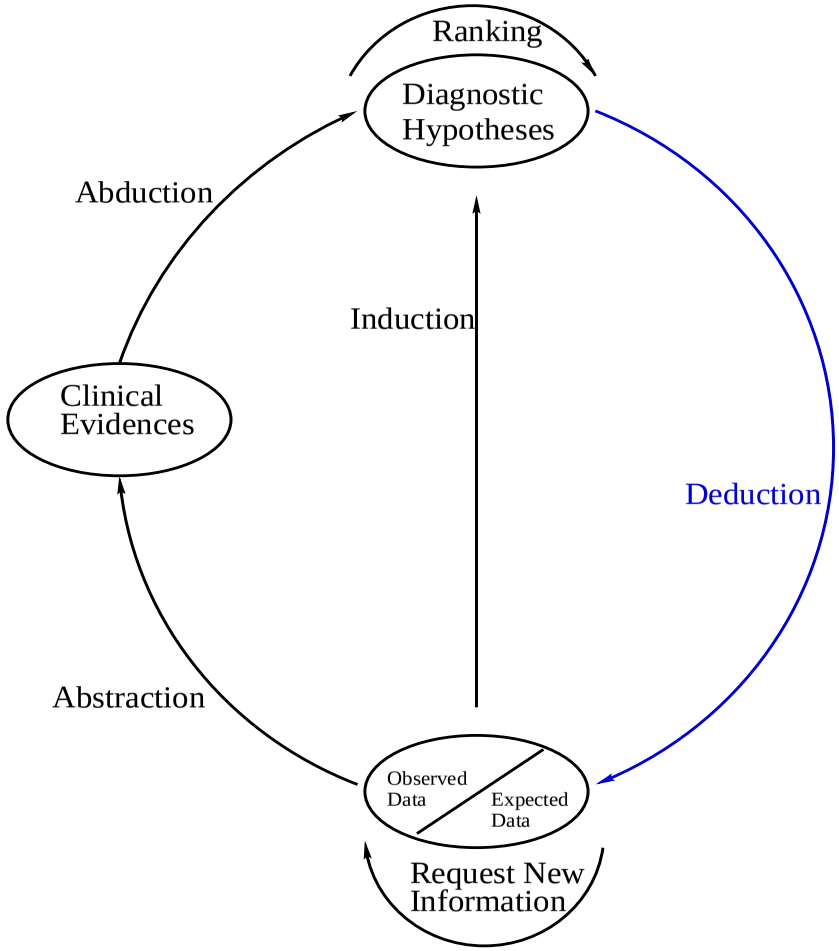
An epistemological model of Medical Reasoning



Causal knowledge expressed through models is exploited in the deductive/inductive phase whereas taxonomic and heuristic knowledge is exploited in the abductive phase

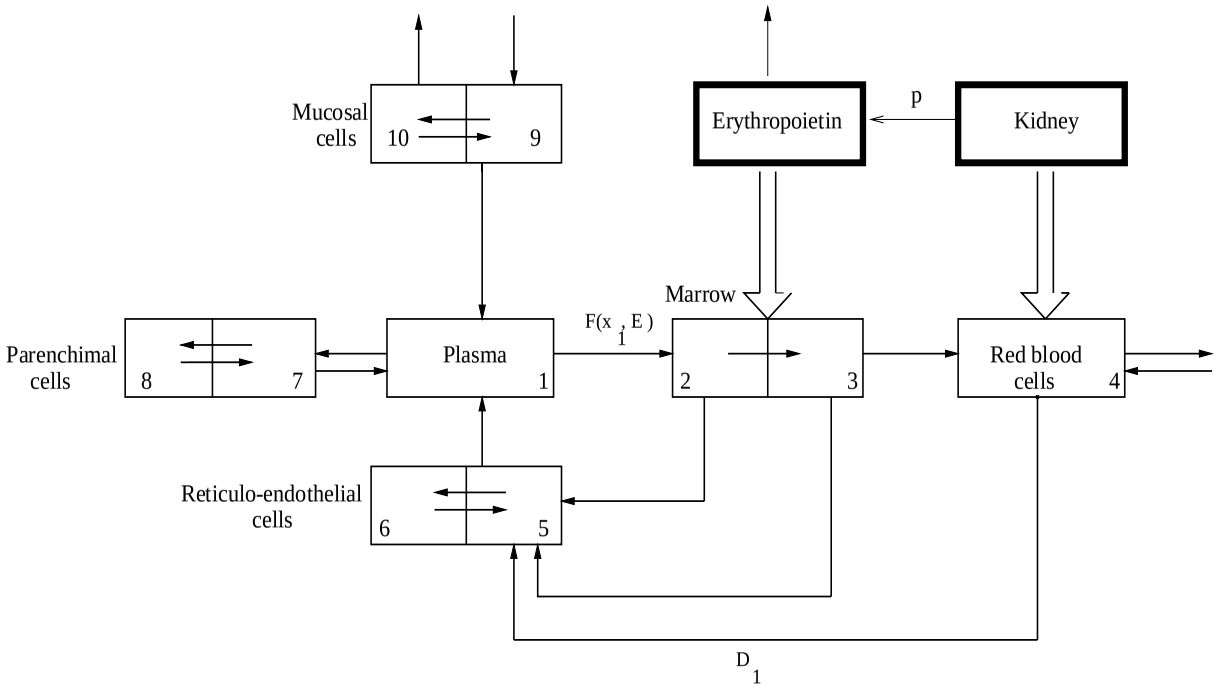
Diagnosis

Diagnosis aims at providing the *best explanation* for the current situation in the patient



Problem: Diagnosis of Anemia

System: Iron Metabolism



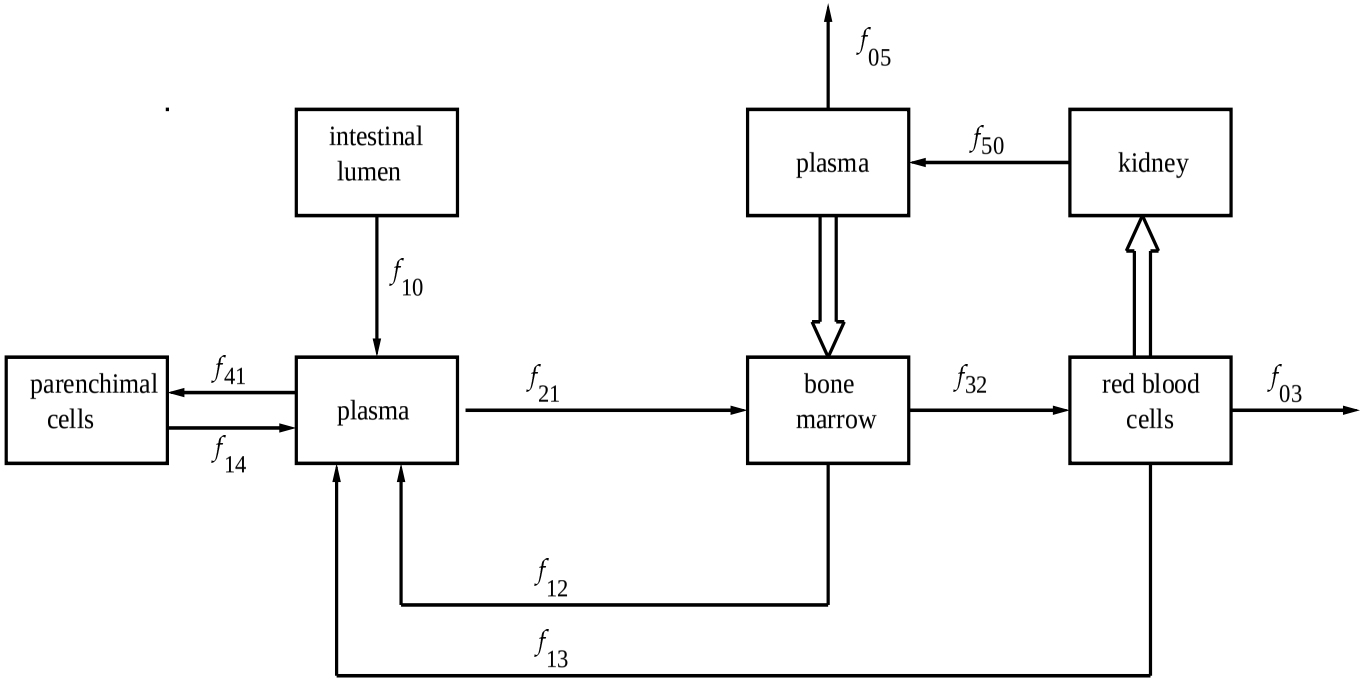
Quantitative formulation

$$\dot{x}_1 = (k_{12}x_1 + F(x_1, E)) + (k_{14}x_5 + k_{13}x_7 + k_{11}x_9)(x_1^* - x_1)^2$$
$$\dot{x}_2 = F(x_1, E) - (k_1 + k_4)x_2$$
$$\dot{x}_3 = k_1x_2 - (k_2(E) + k_3)x_3$$
$$\dot{x}_4 = k_2(E)x_3 + i_1 - D_1(x_3, E, t) - D_0(x_3, E, t)$$
$$\dot{x}_5 = k_4x_2 + k_3x_3 + k_6x_6 + D_1(x_3, E, t) - k_5x_5 - k_{14}x_5(x_1^* - x_1)^2$$
$$\dot{x}_6 = k_5x_5 - k_6x_6$$
$$\dot{x}_7 = k_{12}x_1 + k_8x_8 - k_7x_7 - k_{13}x_7(x_1^* - x_1)^2$$
$$\dot{x}_8 = k_7x_7 - k_8x_8$$
$$\dot{x}_9 = i_2(x_9) + k_{10}x_{10} - k_9x_9 - k_{11}x_9(x_1^* - x_1)^2$$
$$\dot{x}_{10} = k_9x_9 - (k_{10} + k_{15})x_{10}$$
$$\dot{E} = e^{-a_4(x_4(t-\tau)-y_4^*)} - k_{16}E$$

The values of the coefficients in the model are estimated from data collected by injecting radio-active iron.

Remark: A *quantitative* representation is *NOT* appropriate for diagnosis

Iron metabolism: qualitative model

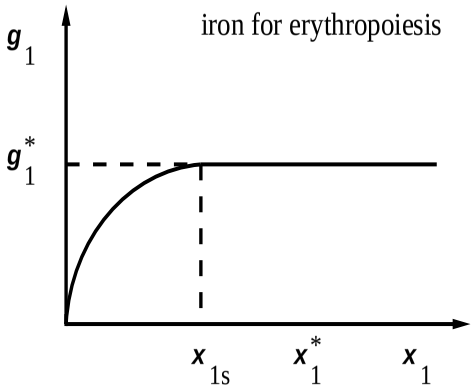


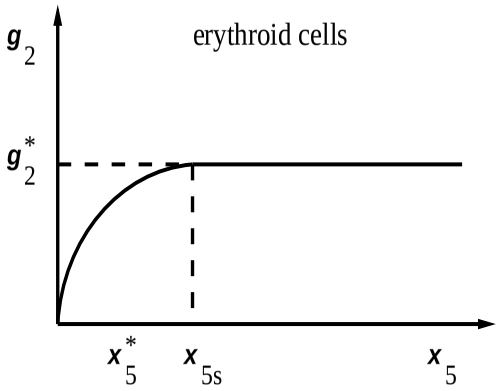
$$\dot{x}_i = f_{i0} + \sum_{\substack{j=1 \\ j \neq i}}^{n} f_{ij}(x_j) - \sum_{\substack{j=1 \\ j \neq i}}^{n} f_{ji}(x_i) - f_{0i}(x_i)$$

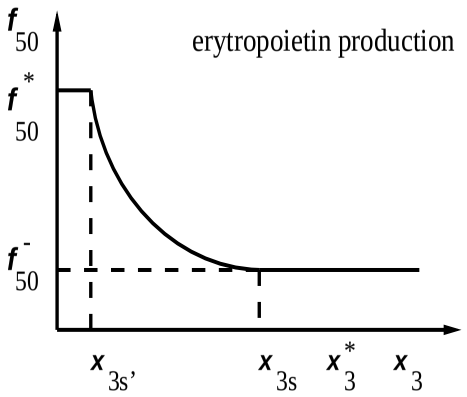
The equations are qualitatively expressed through QDE's in the QSIM formalism

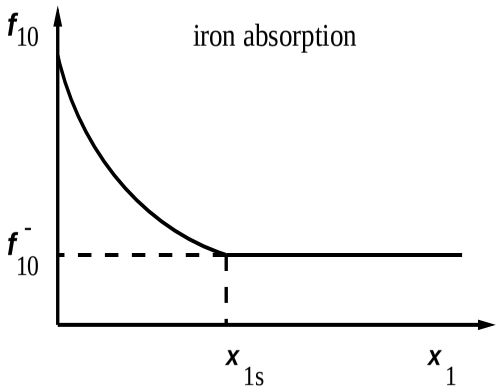
Erythropoietin

$$f_{21}(x_1, x_5) = g_1(x_1) \cdot g_2(x_5)$$









Basic pathophysiological mechanisms

- sudden or chronic blood loss
- defective iron absorption
- failure of the proliferative capacity of the bone marrow
- ineffective erythropoiesis
- peripheral haemolysis
- failure of erythropoietin stimulation

A patient's case picture

Qualitative Abstraction

Patient: Date:

anemia	mild
white.cells.count	normal
mean.cell.volume	microcytic
retics.count	highly.increased
retics.index	highly.increased
serum.iron	decreased
total.iron.bind.capacity	normal
transferrin.saturation	normal

Diagnostic Conclusions

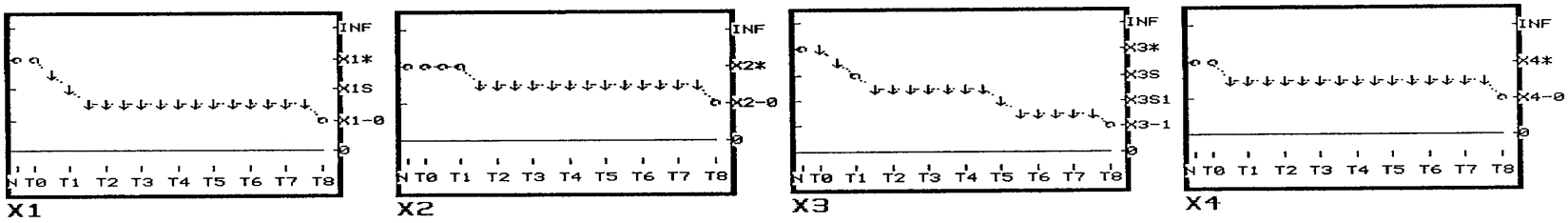
diagnoses are considered in the categories: Definite, Propable, Possible

CHRONIC.DISORDER.WITH.ADJUNCTIVE.CAUSE	PROBABLE
IRON.DEFICIENCY.ASSOCIATED.WITH.ANOTHER.DISEASE	PROBABLE
HEREDITARY.SPHEROCYTOSIS	POSSIBLE

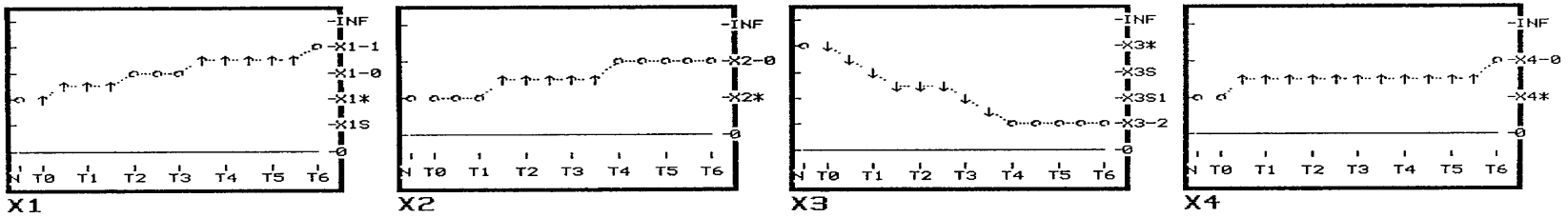
Simulation results (1)

a) chronic blood loss

b) peripheral haemolysis



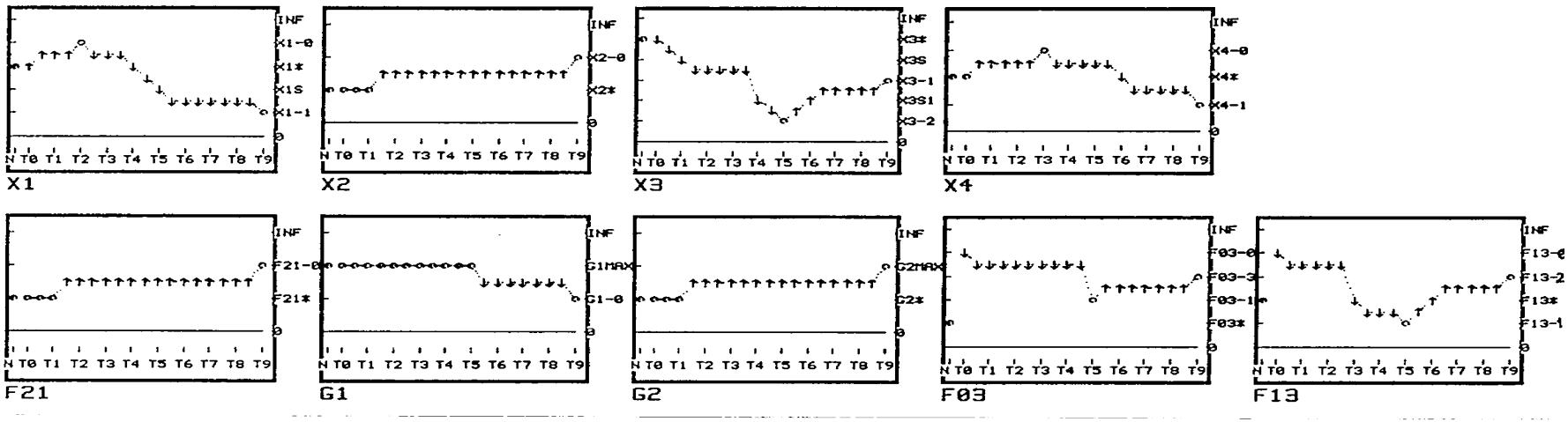
(a)



(b)

Simulation results (2)

c) Chronic blood loss + Peripheral haemolysis



Plausible diagnostic hypothesis

C - Chronic blood loss + Peripheral haemolysis

CLINICAL FINDINGS	OBSERVATIONS	MODEL PREDICTIONS Pathological Model		
		A	B	C
anaemia	decreased	decreased	decreased	decreased
erithroid marrow cellularity	*not observed*	increased	increased	increased
reticulocytes count	increased	decreased	increased	increased
peripheral haemolysis	*not observed*	increased	increased	increased
serum iron	decreased	decreased	increased	decreased
serum ferritin	*not observed*	decreased	increased	decreased

Remarks

1. A *qualitative* representation *IS* appropriate for medical diagnosis
2. *BUT* the development of model-based systems for medical diagnosis is *NOT* a challenging issue due to the lack of interest by the users

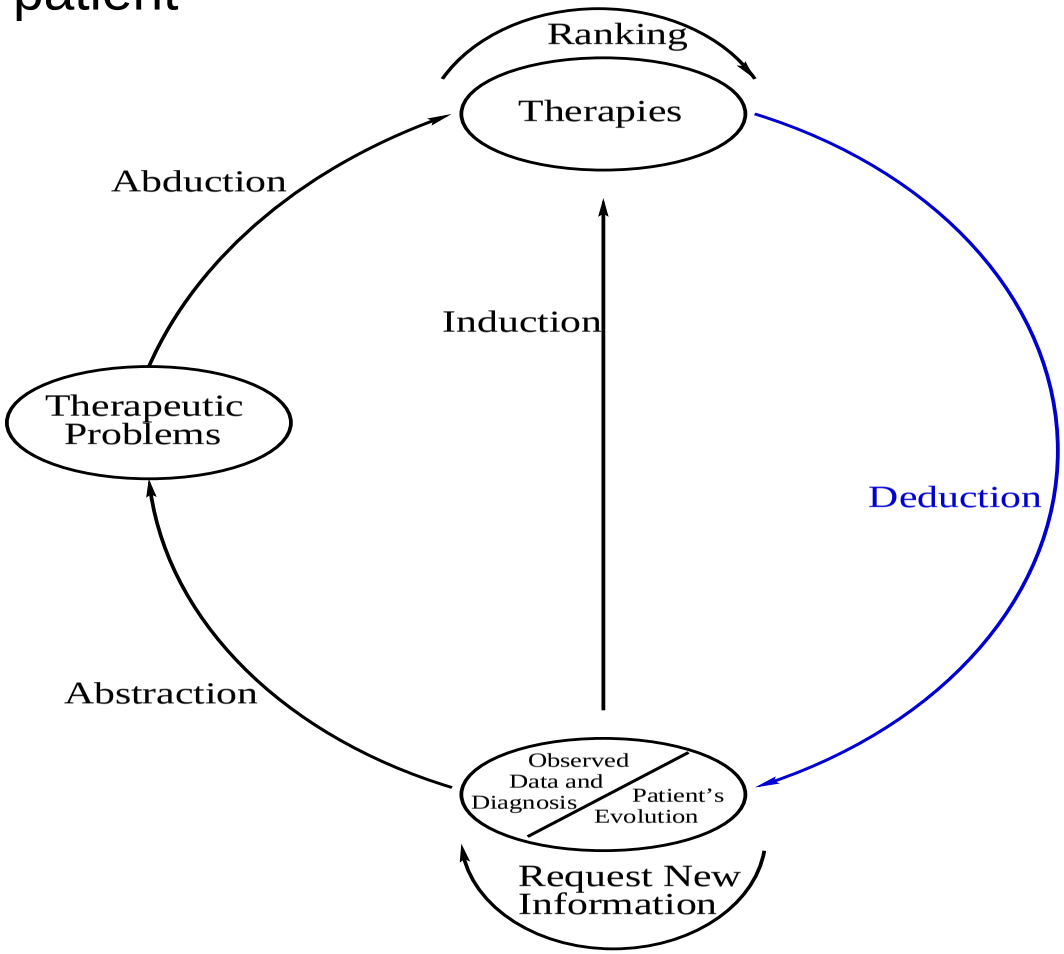
Result of QueryMEDLINE research on Support Decision Systems:

	D	T	M& O
R	6%	41%	53%
DS	53%	19%	28%

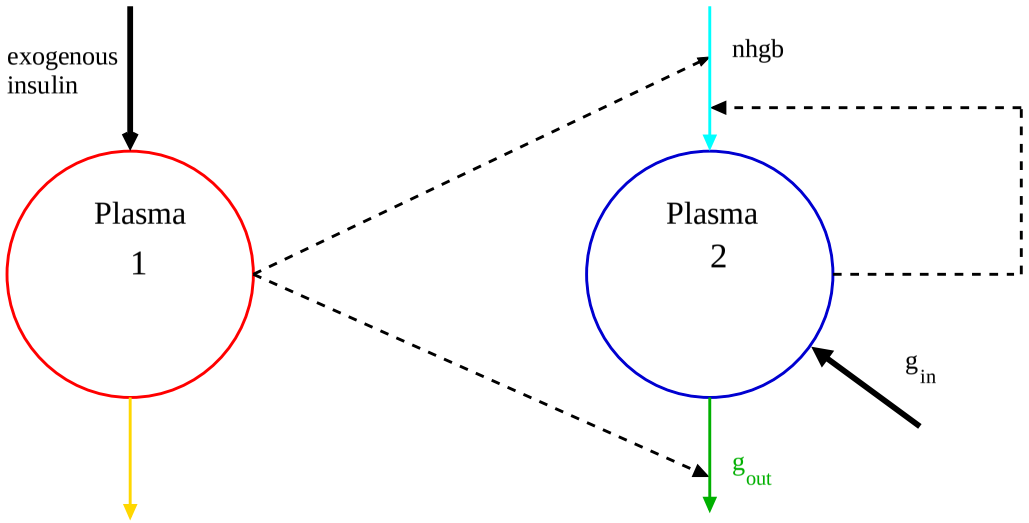
(R= Request for SDS, DS= Developed Systems, D= Diagnosis, T= Therapy, D= Diagnosis, T= Therapy, M& O= Management and Other)

Therapy Planning

Therapy planning aims at adopting the *best action* to improve the current situation in the patient



Problem: Diabetes Mellitus



$$\dot{g} = nhgb(i, g) + g_{in}(t) - g_{out}(i, g)$$

- the insulin dynamics is modelled as its input signal shape
- the Net Hepatic Glucose Balance ($nhgb$) accounts for the liver capability of releasing or up-taking glucose. Its nonlinear dependency both on i and g is incompletely known.

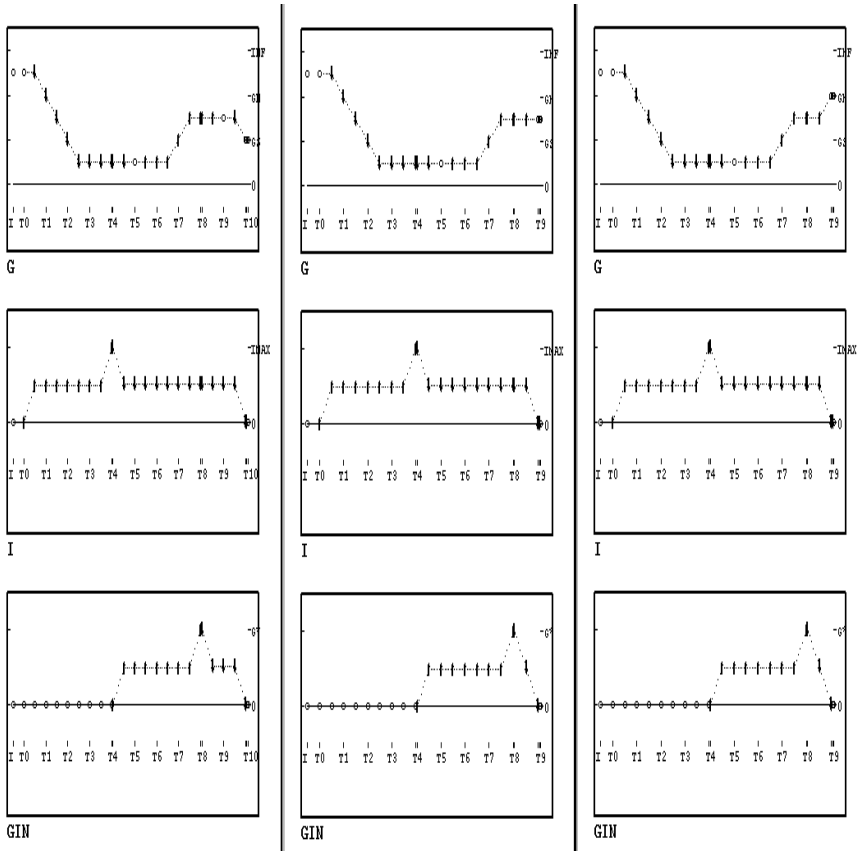
Therapeutical problems

Exogenous insulin therapy should be injiected to provide for the basal insulin need and to compensate for the meal ingestion

1. But which temporal relation between the injection and the meal ingestion ?
2. Which dose of insulin ?

Solution to problem (1)

A *qualitative* model is useful to *test* therapeutic scenarios



Solution to problem (2)

We need for a *quantitative* model to *plan* a therapy

Problem: how do we model $nhgb$?

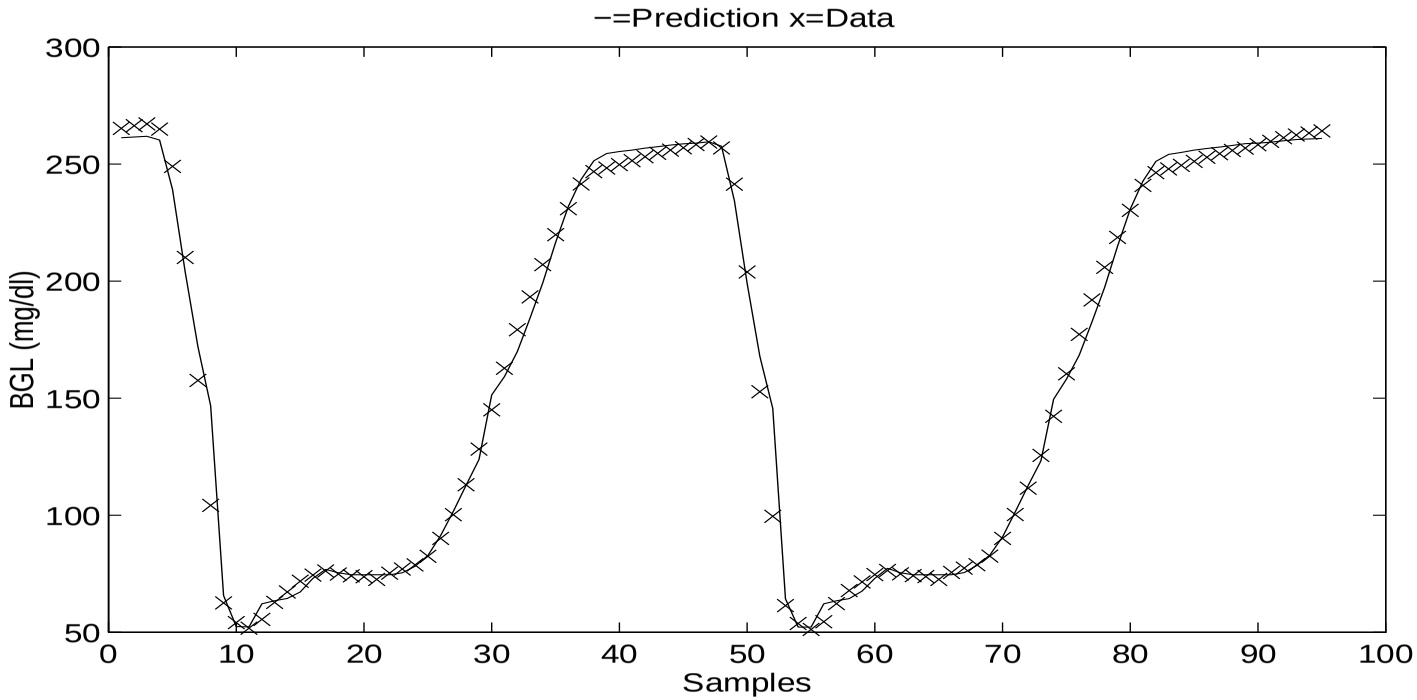
- the linearity assumption is not applicable here
- *tentative* assumptions have been and are tested in the literature
- the nonlinearity may hamper parameter estimation
- the formulation through ODE's is expensive to monitor the therapy

Solution: Exploit the *qualitative* model to build a functional relation which directly links g with the signal inputs i and g_{in}:

$$g(t) = f(i(t), g_{in}(t))$$

Results of the input-output model

A method which combines QSIM models and fuzzy systems is used to approximate f



The input-output model works well as *one-step-ahead* predictor:

$$g_{k+1} = \tilde{f}(g_k, i_k, gin_k) \qquad (3)$$

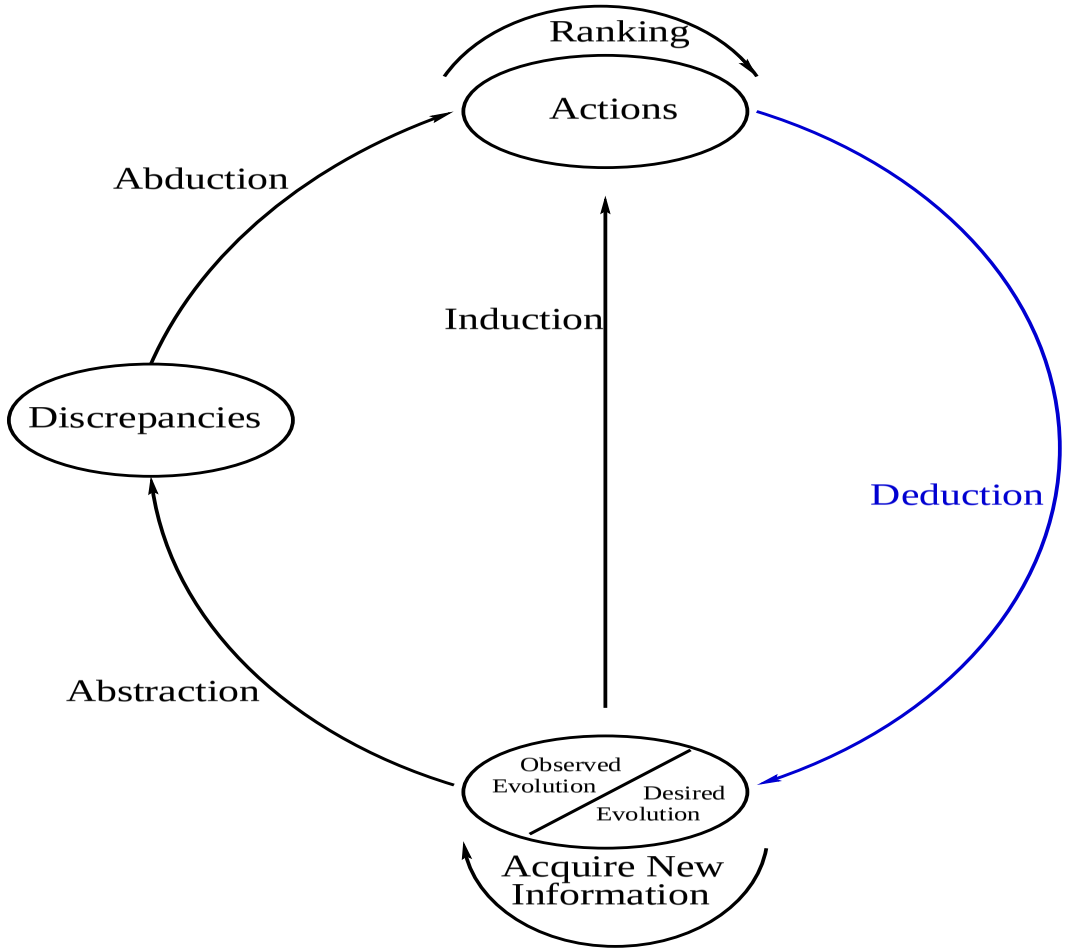
Remarks

- *Qualitative* models are useful for *therapy testing*
- *Quantitative* models are useful for *therapy planning*

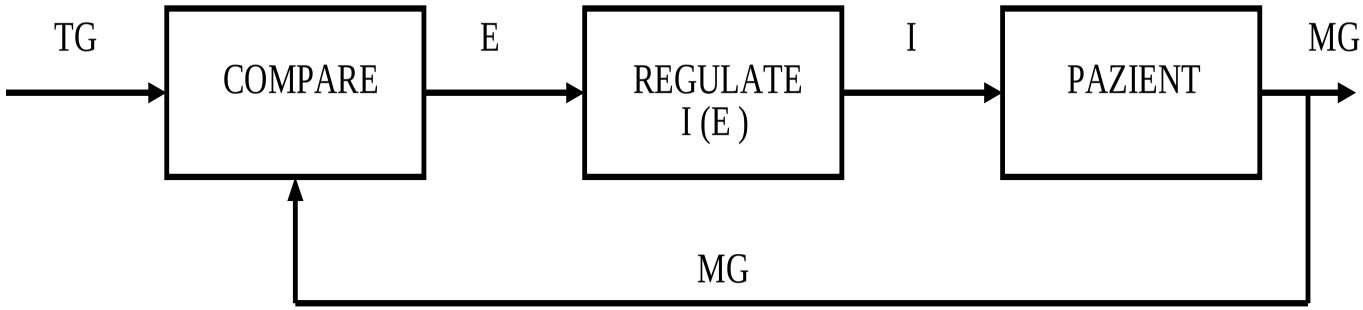
Research problem:
A semi-quantitative approach for therapy planning is also suitable but it needs to be investigated

Monitoring

Monitoring deals with the *control of the evolution* of the clinical state of a given patient under the combined action of a pathogenetic process and/or therapy



Action



TG = : Target Glucose

MG =: Measured Glucose

E=: TG - MG

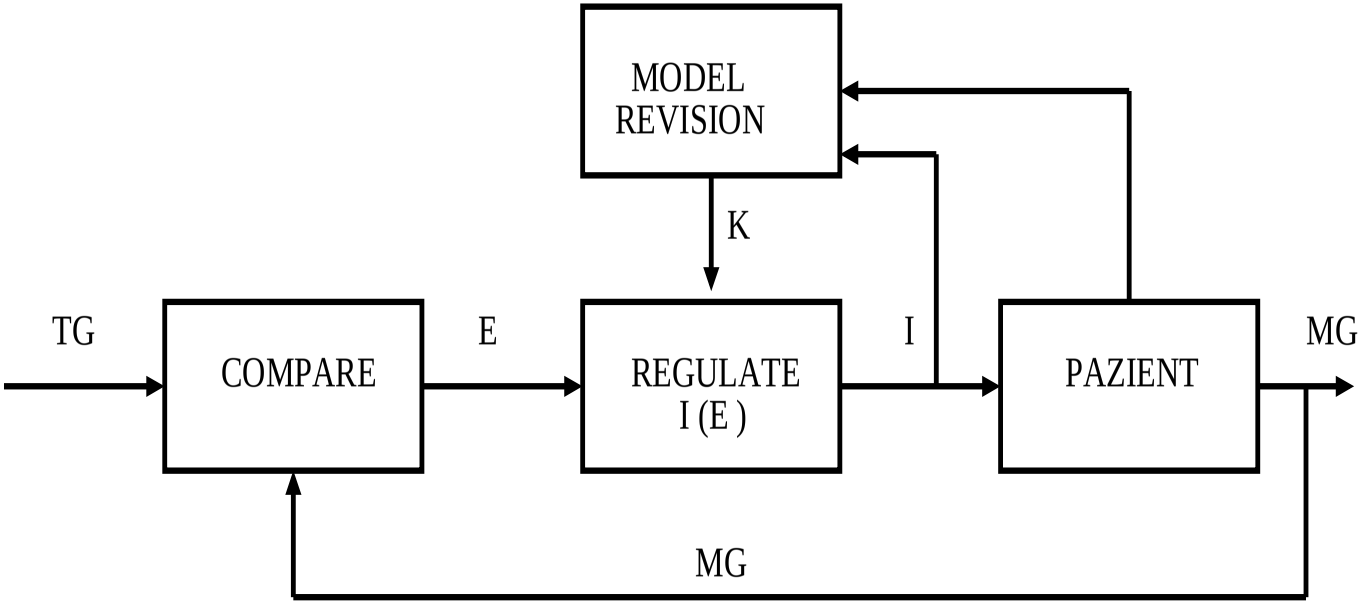
$$I(E) = T_0 - k\,E$$

therapy
I(0)

Monitoring
Action

In our example the action deals with the chance of insulin dose when the discrepancies between the goal and the measured value is different from zero.

Model for controlling the action

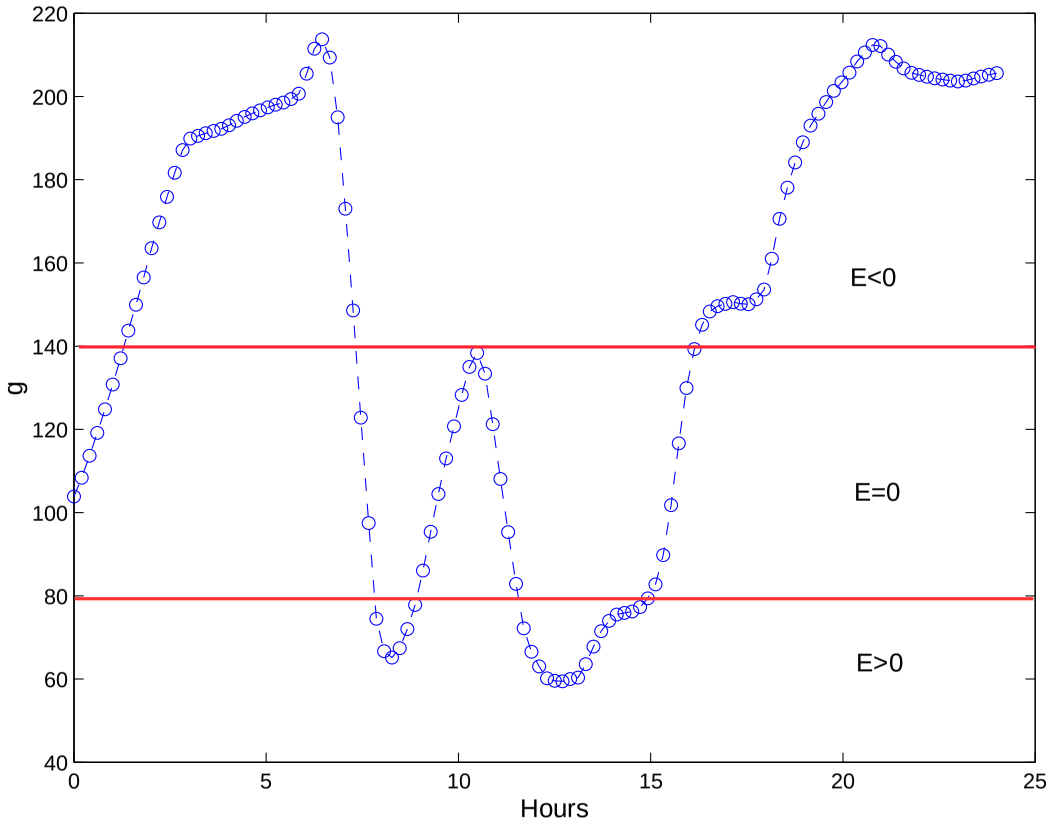


In an adaptive control context, equation (3) becomes:

$$g_{k+1} = f_K(g_k, i_k, g_{in_k}) \qquad (4)$$

Remark

The natural level of model representation for the monitoring task is the *semi-quantitative* one.



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New challenging applications of QR

- Model-based systems for therapy planning and monitoring

  artificial organs (e.g. pancreas)

- Interpretation of physical fields

  interpretation of massive data streams coming from the latest generation medical equipment

- Molecular biology

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