NIDDM:
Evaluation of the Glucose-Insulin Loop

Open- and Closed-Loop Testing
Frequently-sampled Tolerance Curves

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Diabetes Mellitus: Definition

- Loosely Defined:
  Demonstrable hyperglycaemia,
  resulting from ill-defined abnormalities in metabolism
- Absolute deficiency of insulin secretion,
  secondary to (massive) ß-cell lesion and necrosis:
  Type I, IDDM, Ketosis-prone, (Juvenile)
- Insulin secretion (less to more than normal),
  but with target-organ resistance to insulin,
  caused or exacerbated by genetic, dietary, endocrine factors:
  Type II, NIDDM, Obesity associated, (Maturity Onset)

Pre-Test

1. Type II diabetes (NIDDM) is characterized by

- Resistance to the action of insulin
- Deficient insulin secretion

NIDDM is characterized by (fasting) hyperglycaemia, despite (super-)normal insulin levels:

- Elevated glycaemia despite normal insulin levels points to insulin resistance ?

- Failure to increase insulin to normalize glycaemia points to insulin insufficiency / deficiency ?

Pre-Test

1. Type II diabetes (NIDDM) is characterized by

- □ Resistance to the action of insulin
- □ Deficient insulin secretion

2. In Type II diabetes (NIDDM), "fasting" hyperglycemia results from

- ■ Decreased (peripheral) glucose utilisation
- ■ Increased hepatic glucose production

Hyperglycaemia is the new setpoint resulting from an imbalance between

- Push: inappropriate hepatic Glc production ?
- Pull: hampered (Glc- and/or insulin-dependent ?) Glc disposal ?

Pre-Test

1. Type II diabetes (NIDDM) is characterized by

- □ Resistance to the action of insulin
- □ Deficient insulin secretion

2. In type II diabetes (NIDDM), "fasting" hyperglycemia results from

- □ Decreased (peripheral) glucose utilisation
- □ Increased hepatic glucose production

3. In NIDDM, increased "fasting" hepatic glucose output stems from

- ■ Gluconeogenesis
- ■ Glycogenolysis

Fasting hyperglycemia in NIDDM results from
• Inappropriate gluconeogenesis ?

Due to an imbalance of Glycogenesis / Glycogenolysis ?
• Muscle glycogen fuels the gluconeogenic Cori cycle ?
• Liver does not retain gluconeogenic Glc

Why are the questions ambivalent ?

- Who was first, the chicken or the egg ?

Teaching Point:
- to understand role of feedback cycles in metabolic regulation ①

In the light of the "ambivalence" of these questions:

- Why would anyone want to know the answer ? ③
- How would anyone find out what the right answer is ? ②

Teaching Goals of this lesson:
- to understand relevance of the previous questions
- to be able to appreciate research papers on the topic
- to appreciate potential role of the clinical lab in such research

Teaching point 1:
Role of feedback cycles in metabolic regulation

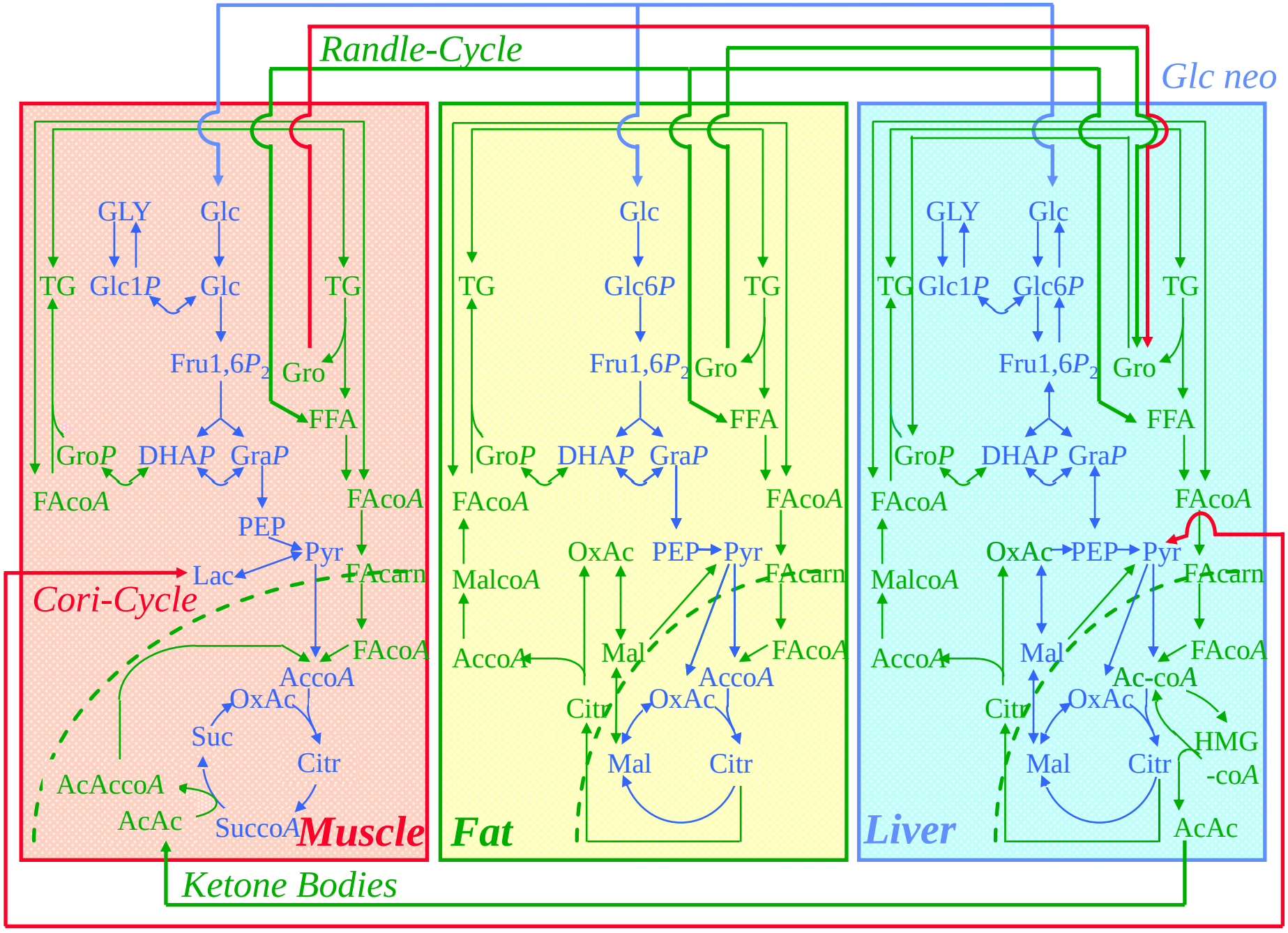
Teaching point 2:
How to find out where the action is ?

Teaching point 3:
How to use what you learned ?

Intermediate Energy Metabolism

Tree Countries
Muscle – Fat – Liver

Two Currencies
Glc – Fat

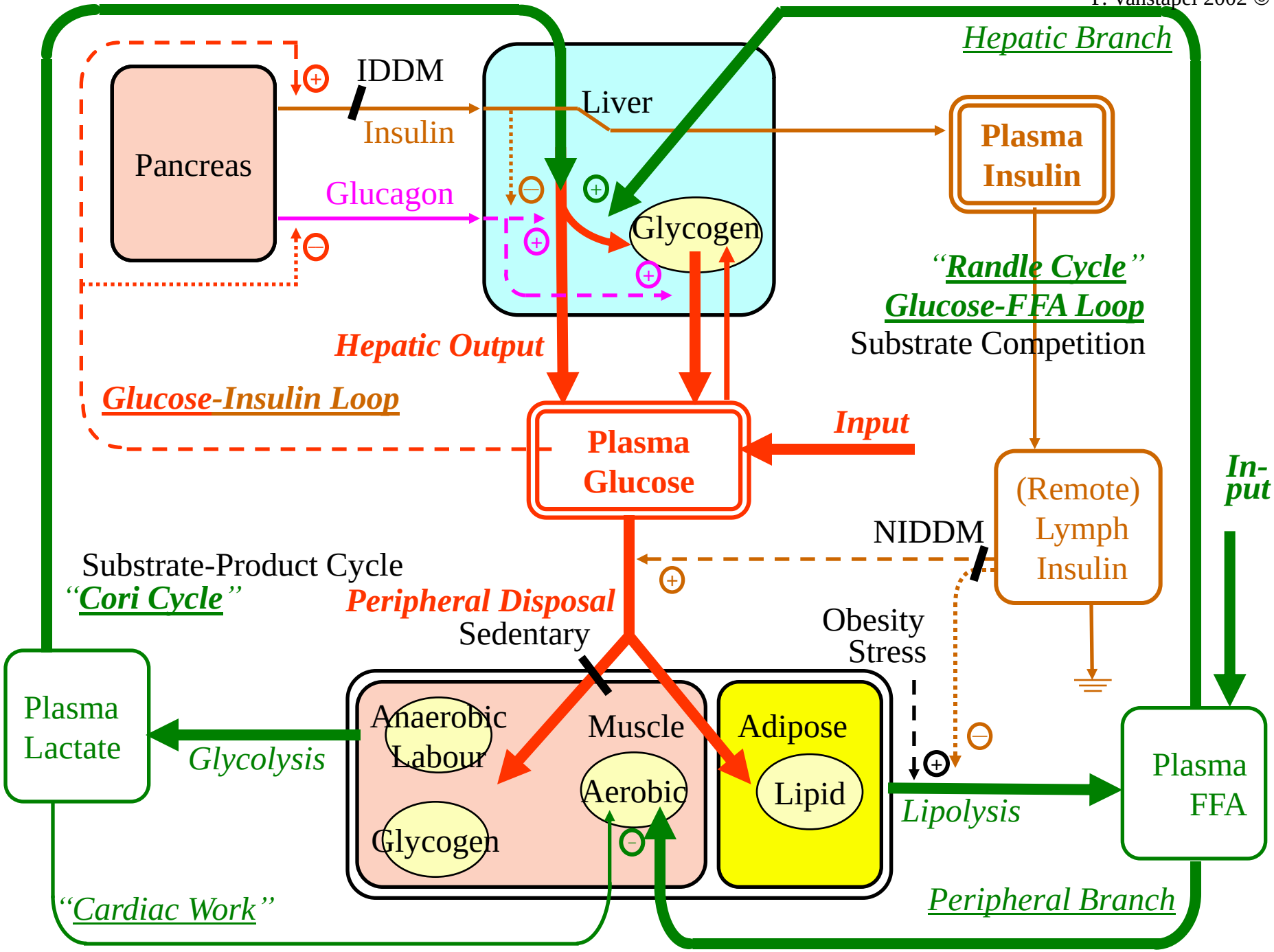


Glc Stock Exchange

Supply & Demand
Producers – Consumers

Tree Countries
Muscle – Fat – Liver

Two Currencies
Glc – Fat



To retain !

- No hormonal regulation without a metabolic machine
  or no use for a throttle without an engine
- Glucagon / insuline balance
  or breaking and giving gas at the same time ?

Paraphrased

- Metabolic regulation is the modulation of cycles
  (while minimizing wasteful futile cycles)
- Hormonal regulation is the modulation
  of autoregulatory properties of metabolism
- Study of the regulatory properties of metabolism
  always has a double focus:
  substrate & hormone dependencies

Desequilibria leading to Disturbed Glc Homeostasis

- Imbalance Insulin / Glucagon (& other counter regulatory hormones)

- Imbalance Glc-production / Glc-deposition

Diabetes:
Pathophysiological hypothesis:

Glc as a driver of Glc-dependent effects

- Glc- and insulin-
  desensitization & irresponsiveness
  (hormonal & metabolic)
- Blood vessel-and nerve-damage
- …

Brownlee
Diabetes **54**:1615-25 (2004)

Evaluating Insulin Action *in Vivo*: Insulin-independent and –dependent Substrate Effects

- Insulin-independent Glc-dependent Glc-effects: $\sim dG\overset{\circ}{l}c / d[Glc]$

  Glc uptake

  - Brain: Saturated at low [Glc]
  - Liver, erythrocytes, renal medulla, gut: not saturated at physiological [Glc]
  - Muscle, fat tissue: "basal" Glc-consumption by insulin-dependent tissues in the absence of insulin

- Insulin-dependent Glc-effects: $\sim dG\overset{\circ}{l}c / d[Insulin]$

  - Interaction Glc & insuline

  NIDDM: "*high glucose despite normal insulin*": insulin "resistance"

  "*despite high glucose insulin normal*": insulin "deficiency"

  - Insulin dependence index:

  Insulin-dependent Glc deposition as a function of insulin levels:

  "insulin sensitivity & responsiveness"

  → extent of the response

  → concentration dependence

Evaluating Insulin Action *in Vivo*: Insulin-independent and -dependent Substrate Effects

- Physiologically relevant interactions:
  - Glc-preserving events during a fast
  - Glc-homeostatic (restorative) events after a Glc load
  - Balance: "Hepatic Glc Output" *versus* (peripheral) "Glc Deposition"

- Available test protocols:
  - Steady-state- (clamps) and challenge (tolerance) tests
  - Open- and closed-loop protocols

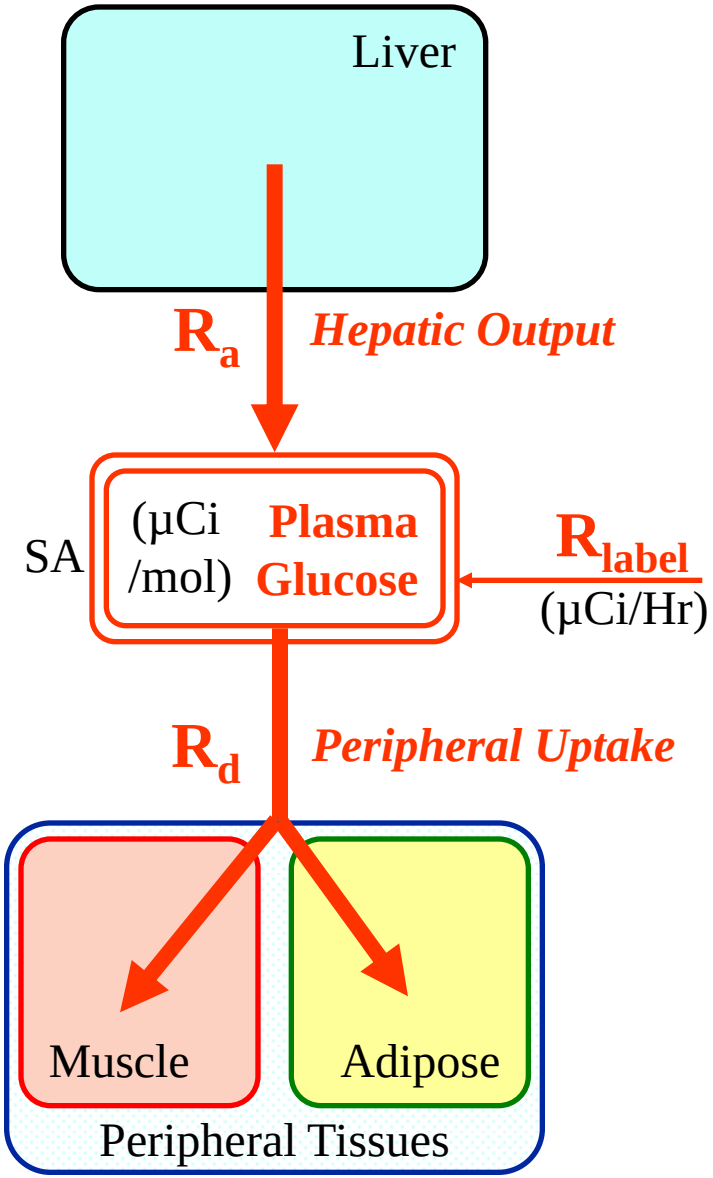
Teaching point 1:
Role of feedback cycles in metabolic regulation

Teaching point 2:
How to find out where the action is ?

Teaching point 3:
How to use what you learned ?

Measuring Rates of Glucose Metabolism

$\mathring{G}lc$



Fick's Dye Dilution Principle

Experimentally measured

Experimentally fixed

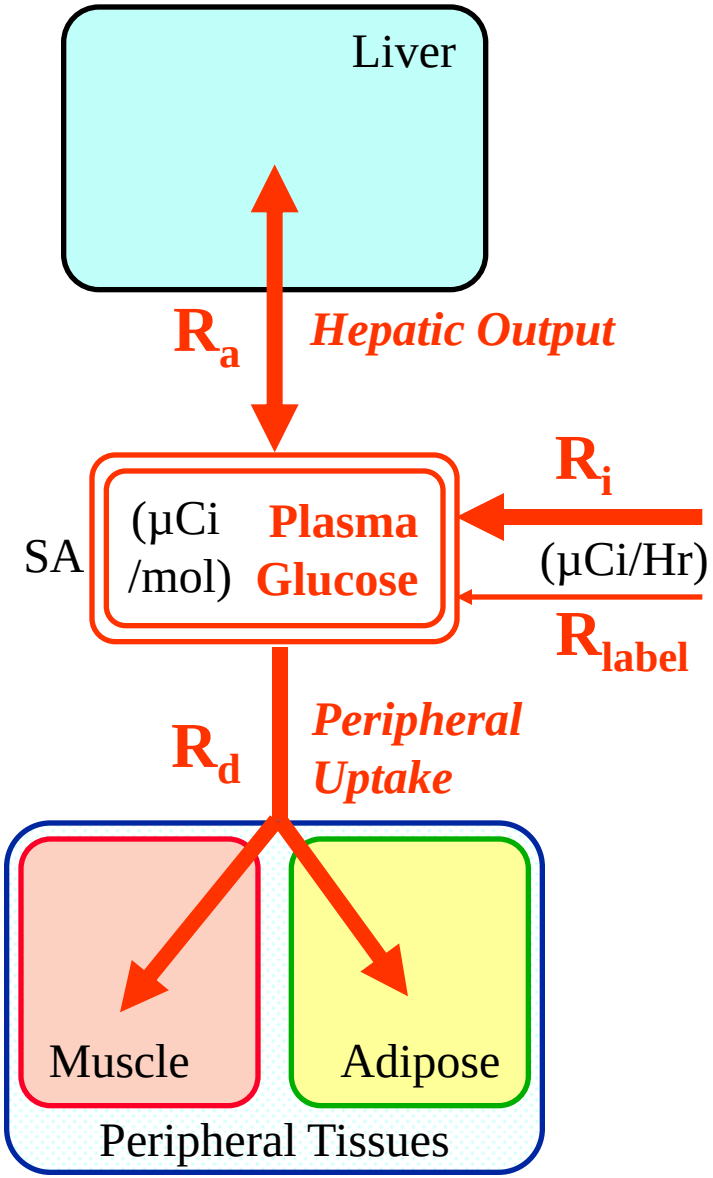
Isotope Dilution:

$SA = R_{label} / R_a$

$R_a = R_{label} / SA$

Steady State:

$R_d = R_a$



Experimental Purpose:
How is Glc load handled ?

Steady State:

$R_d = R_a + R_i$

Isotope Dilution:

$SA = R_{label} / (R_a + R_i)$

$R_a = (R_{label} / SA) - R_i$

$R_d = R_a + R_i$

$R_a = f(R_i)$; $R_d = g(R_i)$

Indirect Calorimetry

3 measured parameters

Oxidized Substrate	Respiratory Quotient	Urinary Nitrogen
	[CO_2/O_2]	[µmol/Hr]
Carbohydrate	1.000	-
Lipid	0.707	-
Protein	0.796	rate

3 unknowns

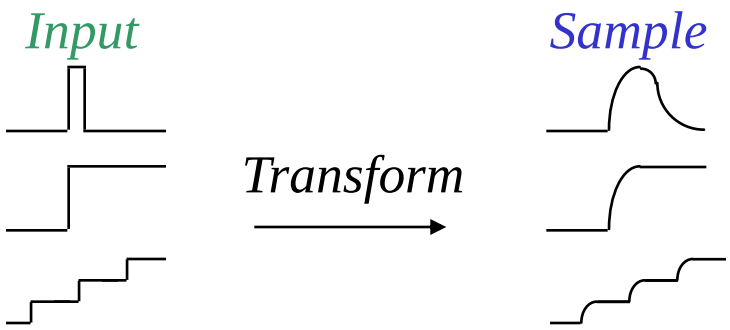
R_{ox} : oxidative Glc disposal

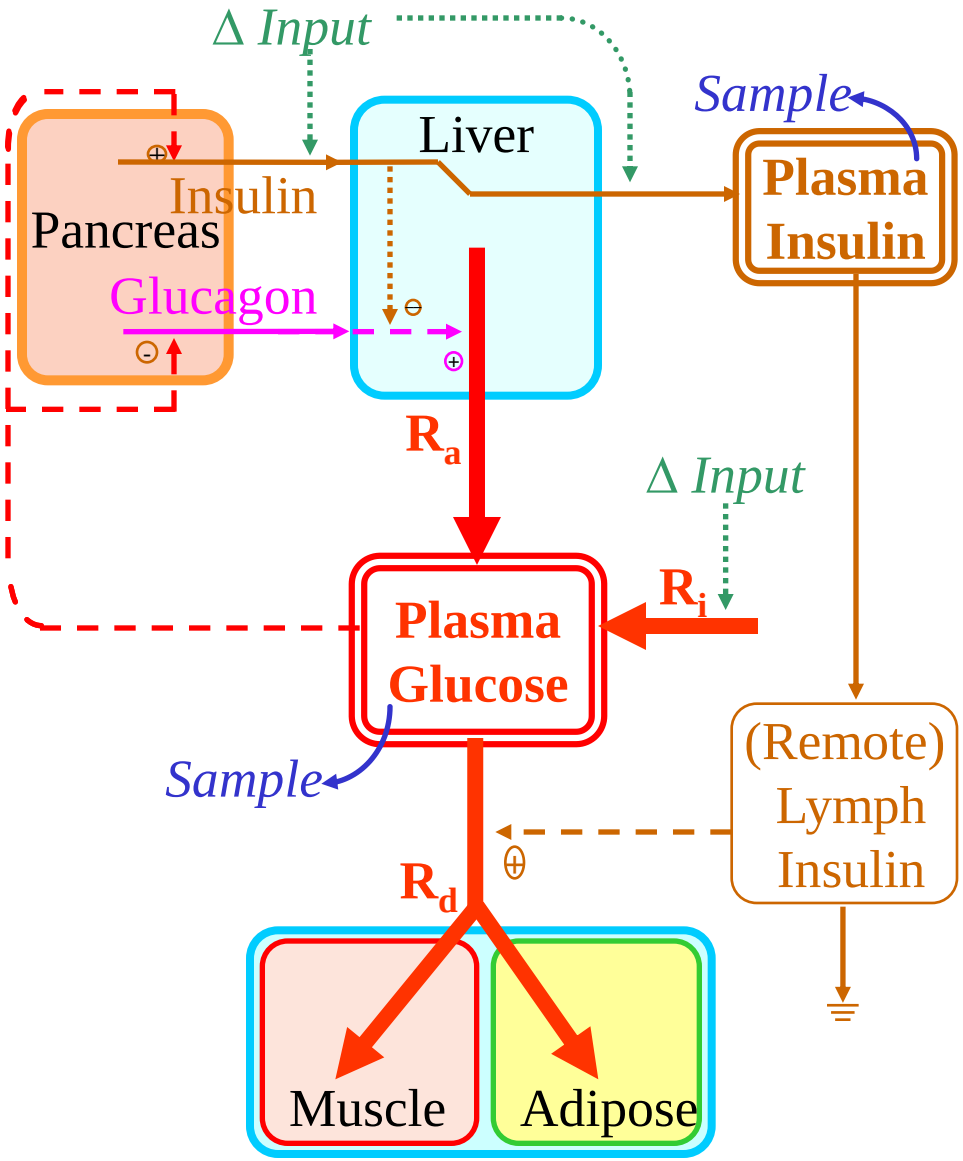
$R_d - R_{ox}$: non-oxidative Glc disposal
= (peripheral) Glycogen deposition
+ glucosuria

Evaluating the Glc-Insulin Loop

Insulin-Glucose Loop

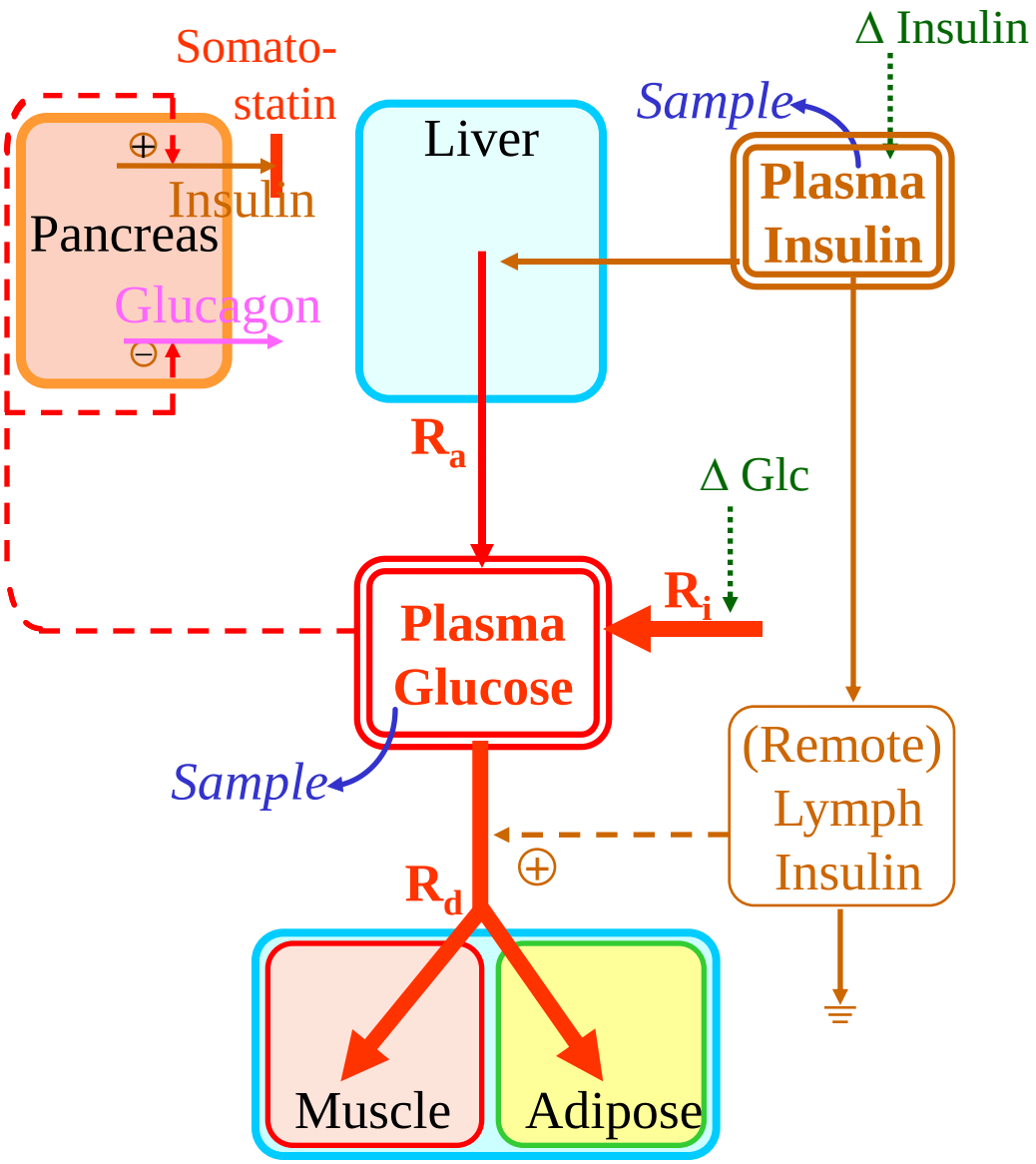
- Plasma Glc levels: resultant of
  R_a: Hepatic Glc Output
  R_d: (Peripheral) Glc disposal
  R_i: Glucose input (infusion)
- Plasma Glc levels are regulated by an insulin feedback cycle
- Test system
  by infusion of Glc and insulin
- Sample plasma compartment to evaluate
  insulin and Glc responses of the system





Open Loop: Insulin Suppression Test

- Somatostatin blocks endogenous glucagon / insulin secretion
- Infuse
  Δ Glc and Δ Insulin
- Evaluate steady-state glycaemia and insulinaemia
- Assess:
  Glycaemia / Insulinaemia at steady-state is non-linear function of
  - Insulin sensitivity & responsiveness
  - Glc-mediated (insulin-independent) Glc disposal



Evaluating Insulin Efficacy:

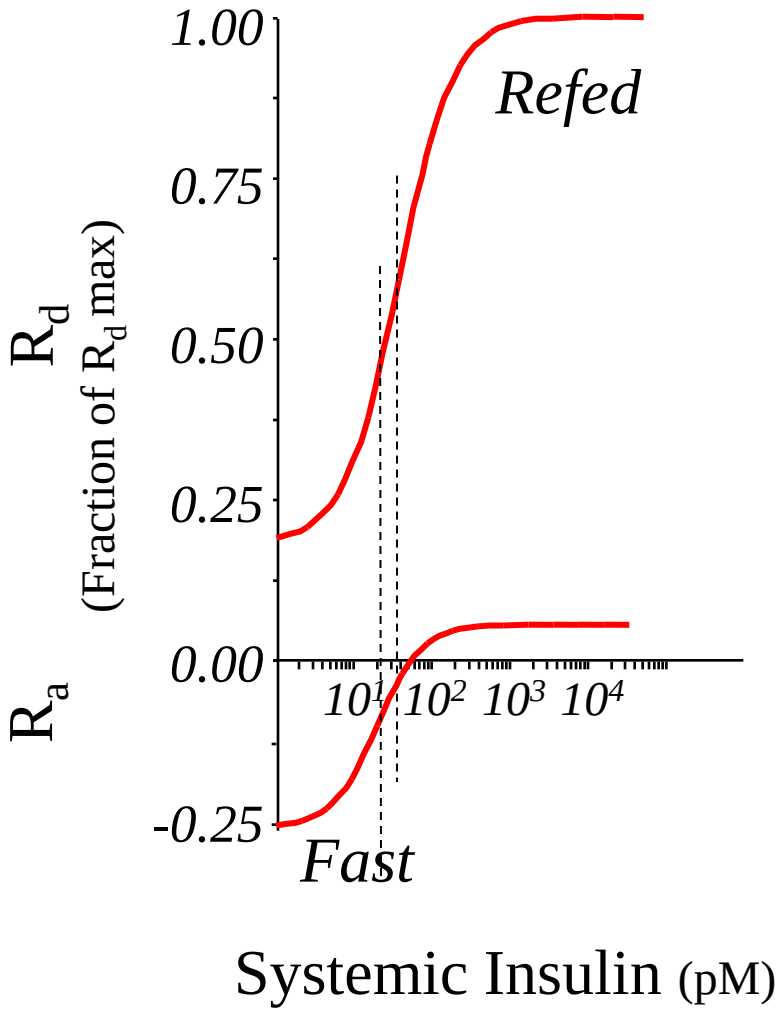
Dose Effect Curves

Insulin Efficacy

The Glc lowering effect of insulin results from modulation of

R_d : peripheral glucose-disposal

R_a : hepatic glucose-output



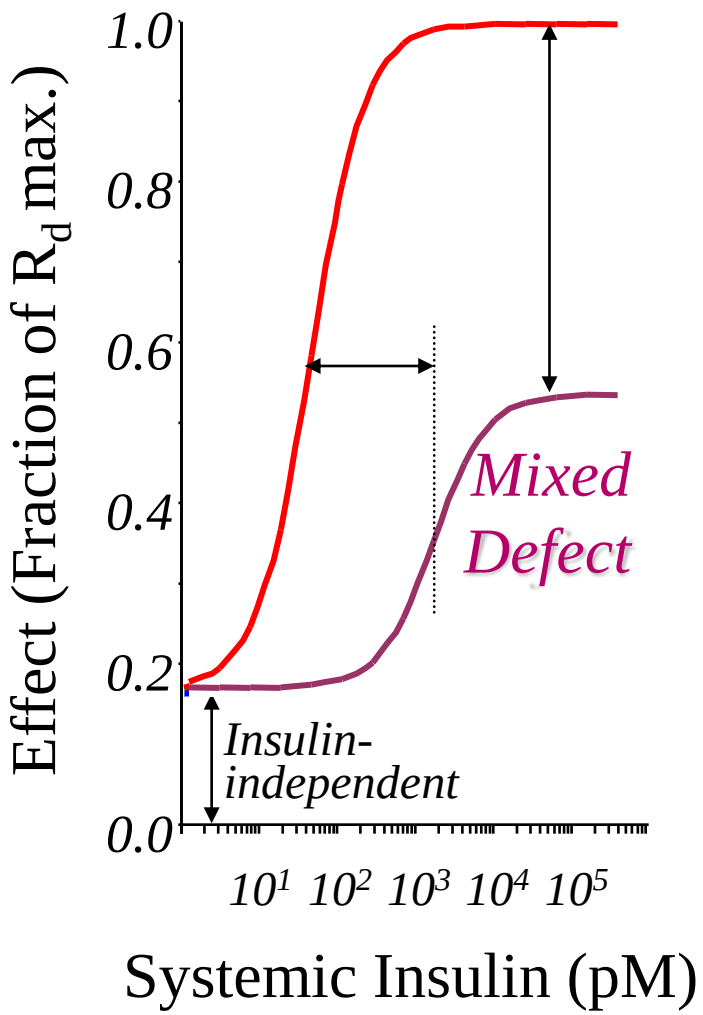
Insulin Efficacy

Insulin efficacy
depends on

- Insulin-responsiveness
- Insulin-sensitivity

Mixed defect
Desensitization due to overexposure ?
Overexposure due to decreased responsiveness ?
Reduced responsiveness due to desensitization ?
Desensitization due to …

Cause and Effect ?

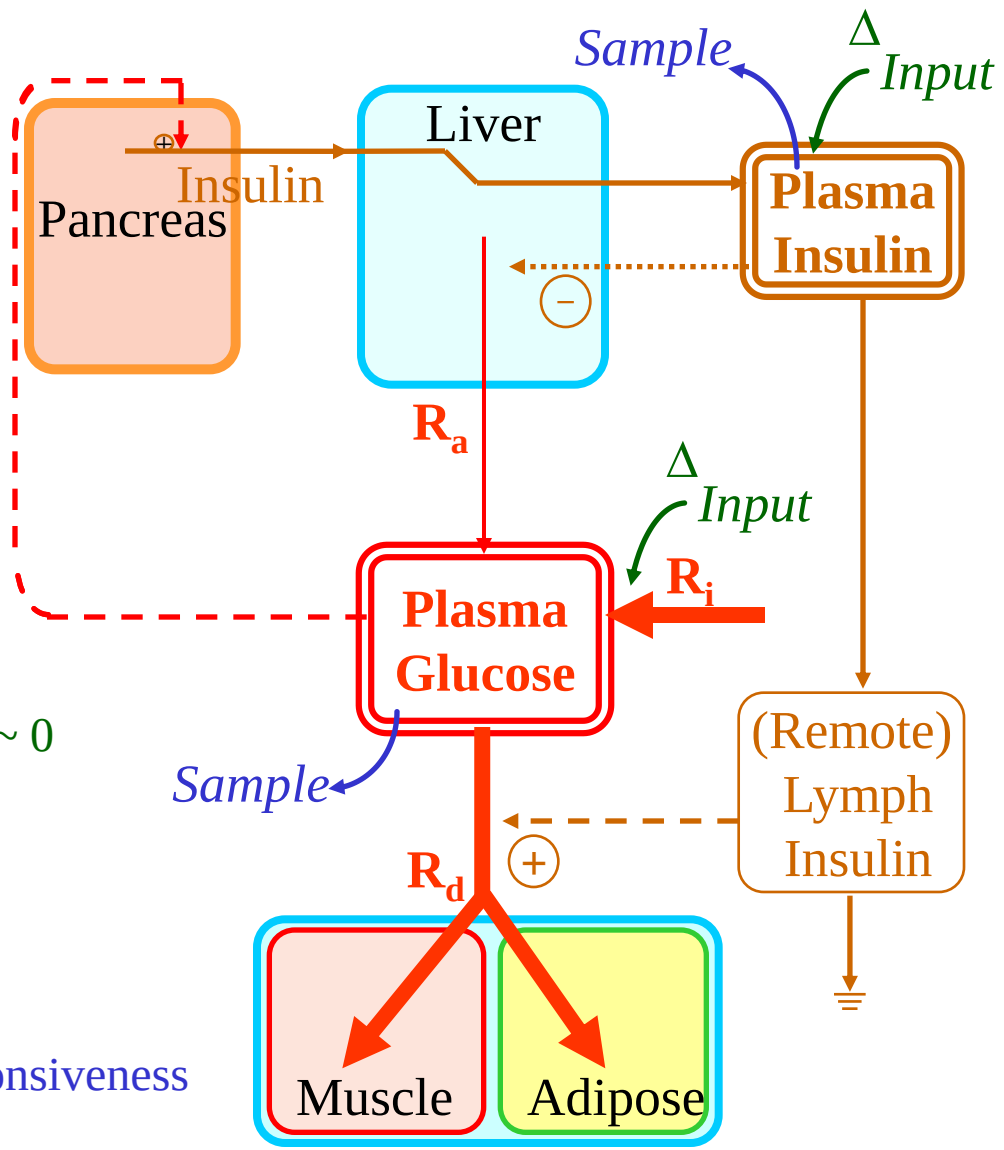


Evaluating the Glc-Insulin Loop:

Variants on the Open Loop Design

Open Loop: Euglycaemic Hyperinsulinaemic Clamp

- Infuse Insulin to clamp insulinaemia > basal level
  - hyperinsulinaemia suppresses Hepatic Glc Output: $R_a = 0$
- Artificial Pancreas:
  for different levels of insulin:
  adjust Δ Glc infusion (R_i)
  to maintain euglycaemia
  - since $R_a = 0$, whence $R_d = R_i$
  - euglycaemia: Glc-dependent effects ~ 0
- Evaluate at steady-state correlation glycaemia and insulinemia
- Assess:
  R_i / [Insulin] is reflection of
  - Peripheral insulin sensitivity & responsiveness
  - Euglycaemia:
    minimal Glc-mediated Glc disposal



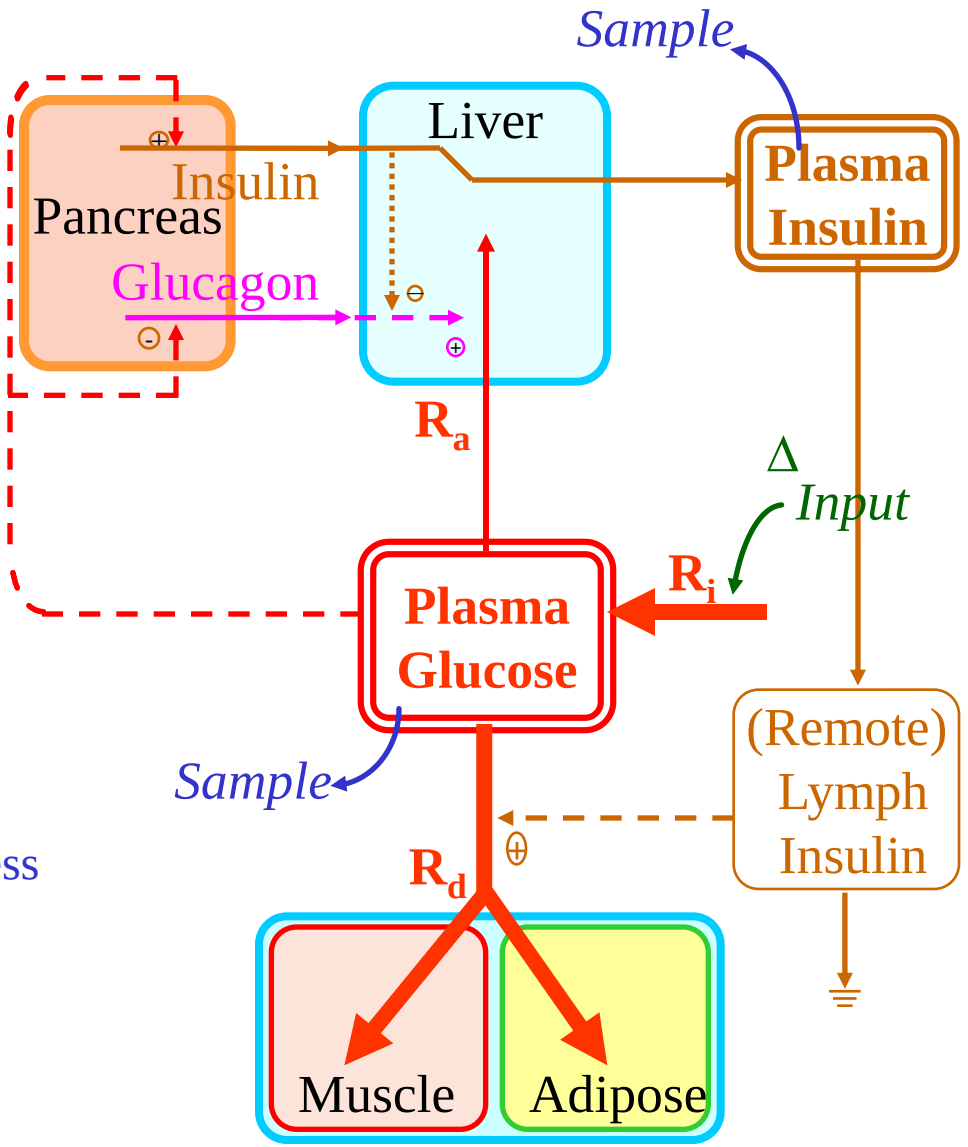
Open Loop: Hyperglycaemic Clamp

- Infuse Glc to <u>clamp</u>
  basal level < <u>glycaemia</u> < renal T_m
  - suppresses Hepatic Glc Output
    $R_a = 0$

- *Artificial Pancreas*:
  <u>Adjust</u> (Δ) Glc infusion (R_i)
  to achieve desired glycaemia

- Correlate (at steady state):
  R_i, insulinaemia, hyperglycaemia

- Assess:
  - R_i / [Insulin]:
    Insulin sensitivity & responsiveness
  - [Insulin] / [Glc]:
    Pancreatic Glc responsiveness
    Glc-stimulated insulin secretion

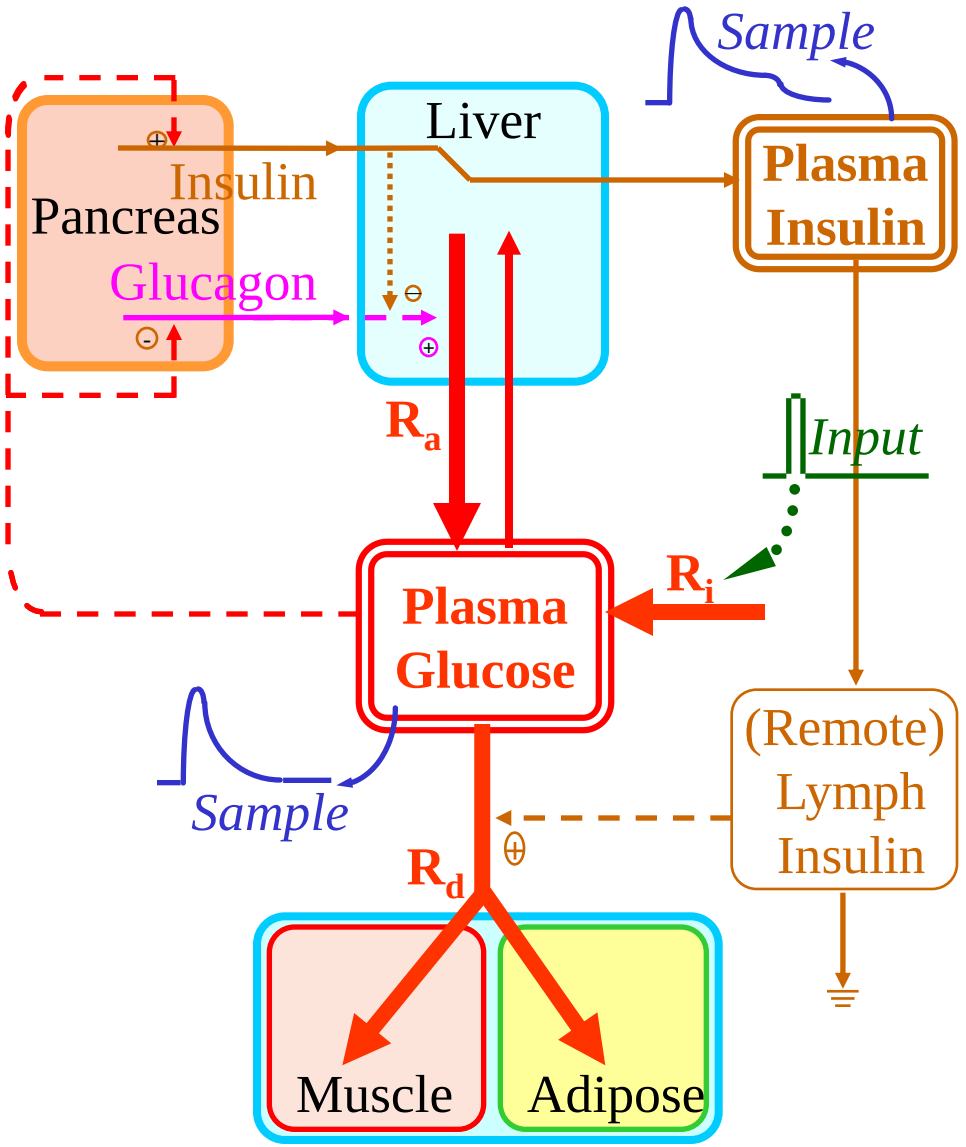


Evaluating the Closed Glc-Insulin Loop:

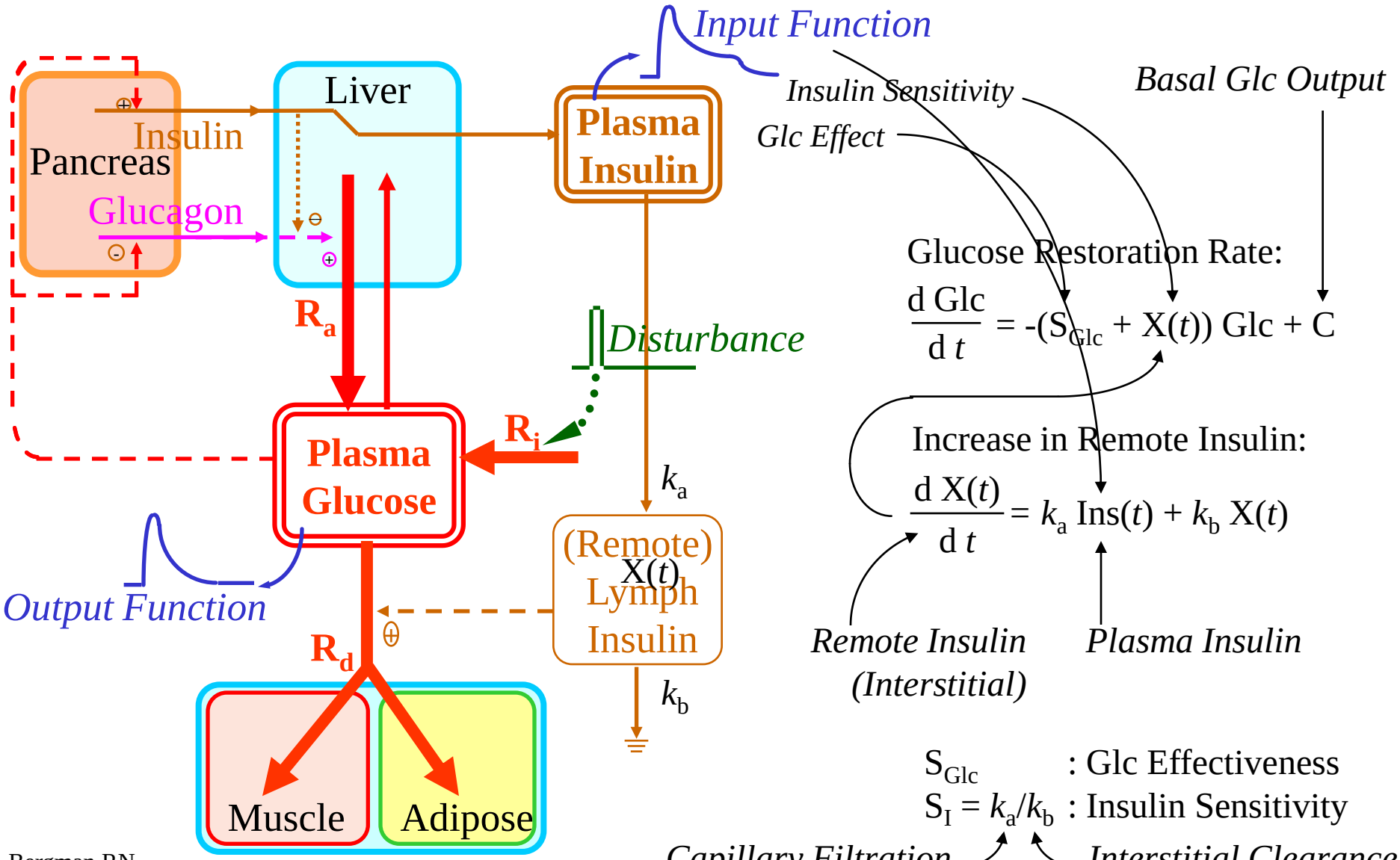
Tolerance Curves

Closed Loop: Intravenous Glucose Tolerance Test

- Infuse bolus Glc
- Evaluate: transient Insuline-Glucose homeostatic response
- - Standardized “physiologic load”
  IV bolus
  - Evaluates pancreatic response
  Early and late phase
  - Test requires functioning pancreas
  (Only NIDDM)
  - Analysis Homeostatic Control:
  Model-dependent analysis



Closed Loop: Intravenous Glucose Tolerance Test



Bergman RN
Diabetes **38**:1512-27 (1989)

Teaching Point

- Study of the regulatory properties of metabolism
  always has a double focus:
  substrate & hormone dependencies

Paraphrased

- Meaningful analysis of the Glc-Insulin loop requires
  substrate (Glc) & hormone (Insulin) measurements

Cave

- I did not say:
  Effective treatment requires
  meaningful analysis of the Glc-Insulin loop

Variants on Tolerance Tests

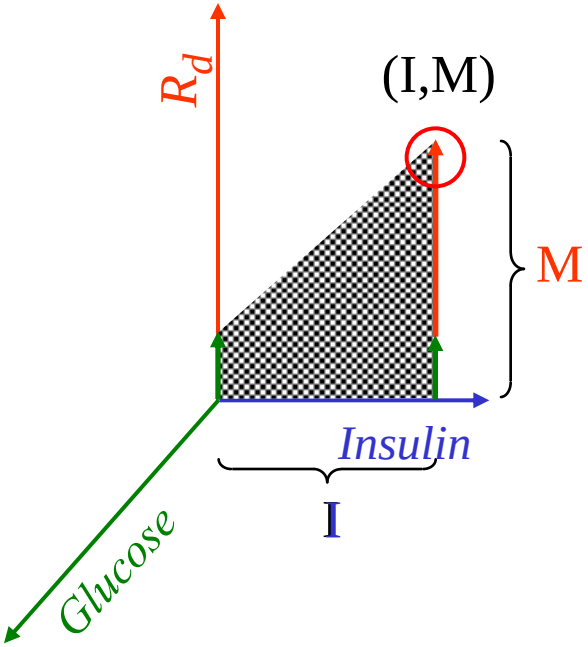
- Glc tolerance
  - tests pancreatic responsiveness to Glc
- Glc + Tolbutamide:
  - tests pancreatic secretory capacity
  - portal Insulin administration
- Glc + Insulin:
  - test becomes possible despite failing Insulin secretion (IDDM)
  - peripheral Insulin administration
    - Increased dynamic range of Insulin
    - *CAVE*: Hypoglycaemia

Comparison

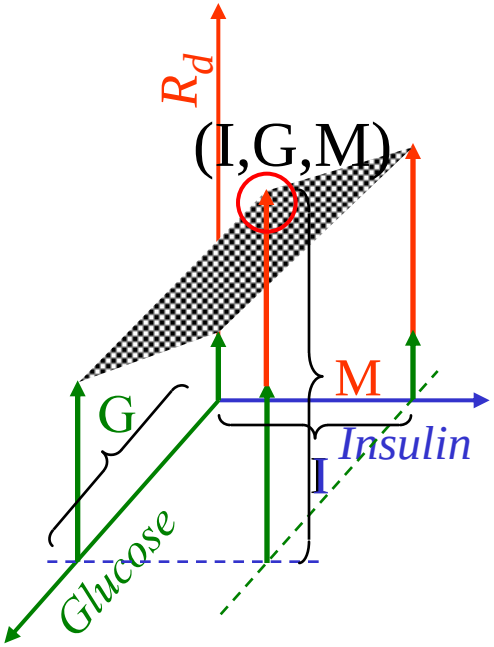
Clamps
&
Tolerance Curves

Comparison Clamps and I.V. Tolerance Test

Static Measurements		Dynamic Measurement
Euglycaemic Clamp	Hyperglycaemic Clamp	I.V. Tolerance Test

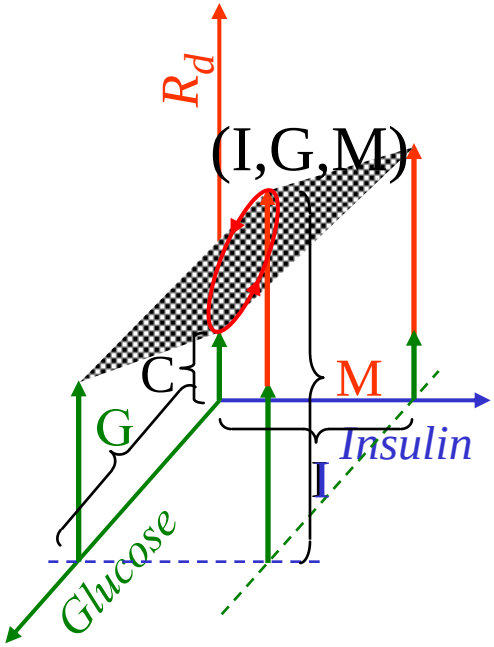


M/I: peripheral insulin responsiveness



M/I: ~ peripheral insulin responsiveness (+ Glc effectiveness)

I/G: pancreatic Glc responsiveness



Dynamic Response: Range of (I,G,M) as f(t) allows extraction: S_{Ins}, S_{Glc}

Scheen AJ *et al*, *Diabetes Metab Rev* **10**:151-88 (1994)

Teaching point 1:
Role of feedback cycles in metabolic regulation

Teaching point 2:
How to find out where the action is ?

Teaching point 3:
How to use what you learned ?

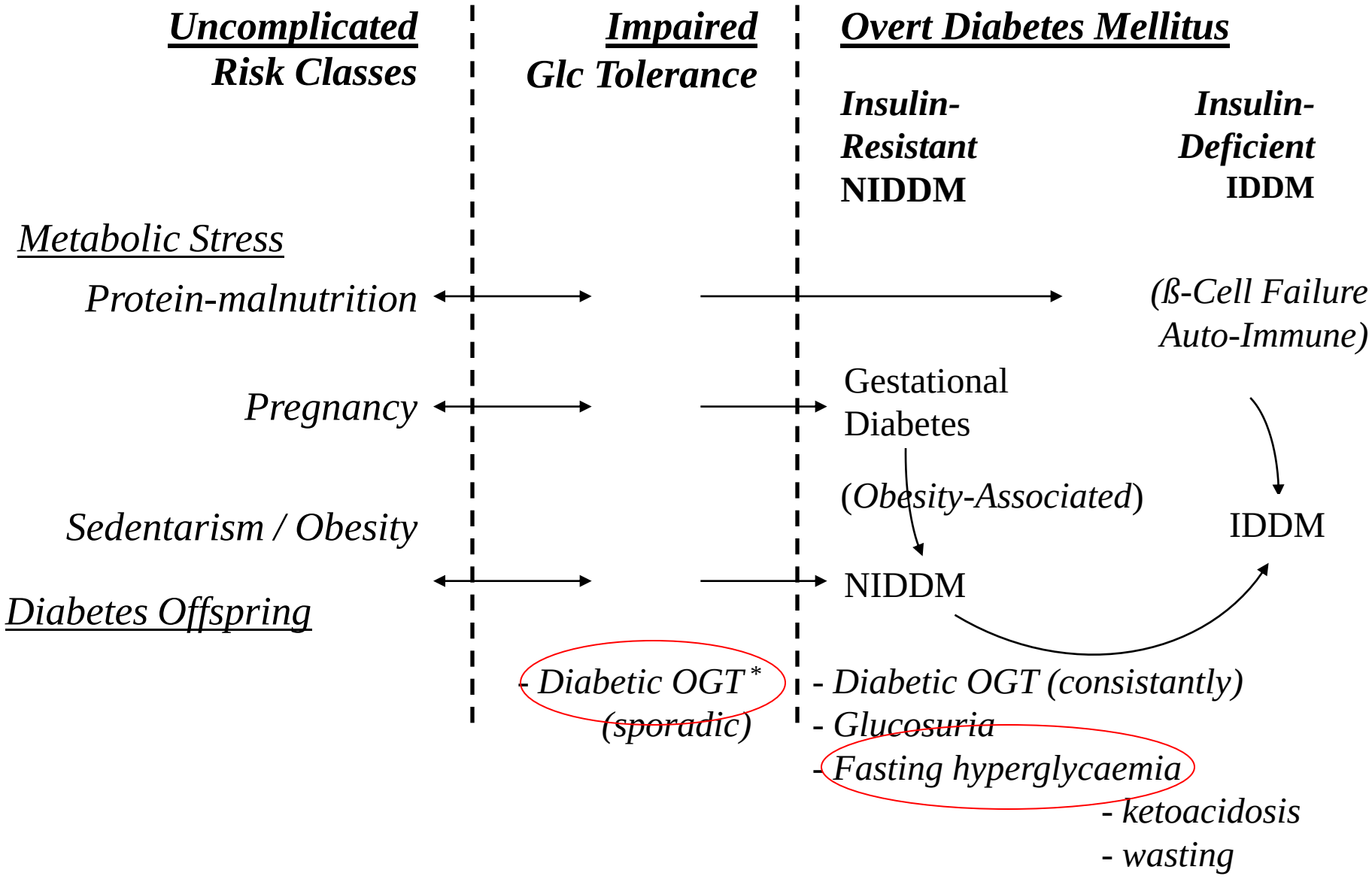
Why bother ?

What is the natural history of the disease ?

Elevated Fasting Glc = Disturbed Postprandial Glc ?

How do medicinal interventions work ?
Directly & Indirectly ?

Diabetes Mellitus: Diagnostic Categories



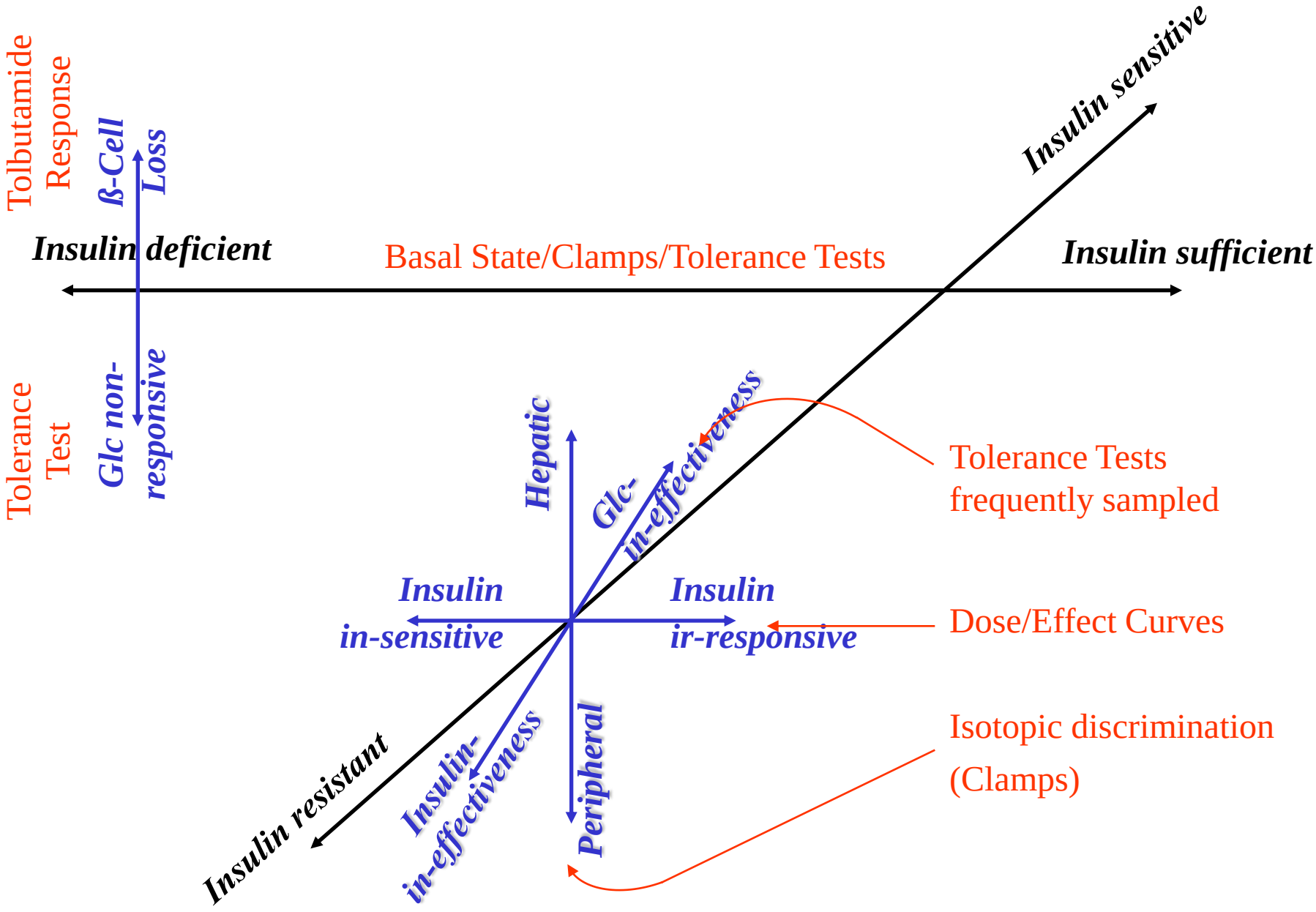
* *OGT: oral glucose tolerance test*

Do Clamp and Tolerance Protocols address Relevant Questions?

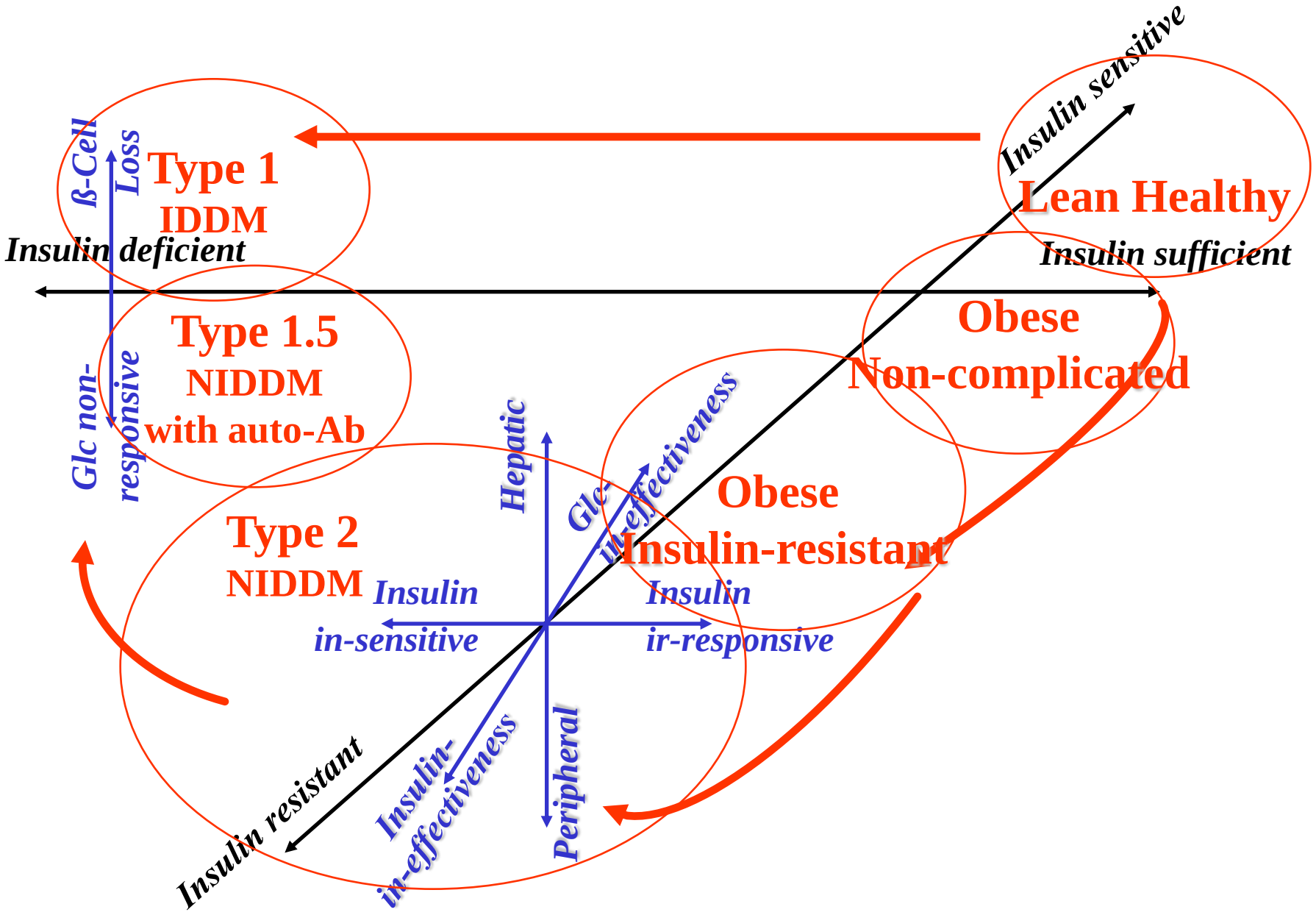
Pathology Staging & Therapeutic Interventions

Clamping Patients

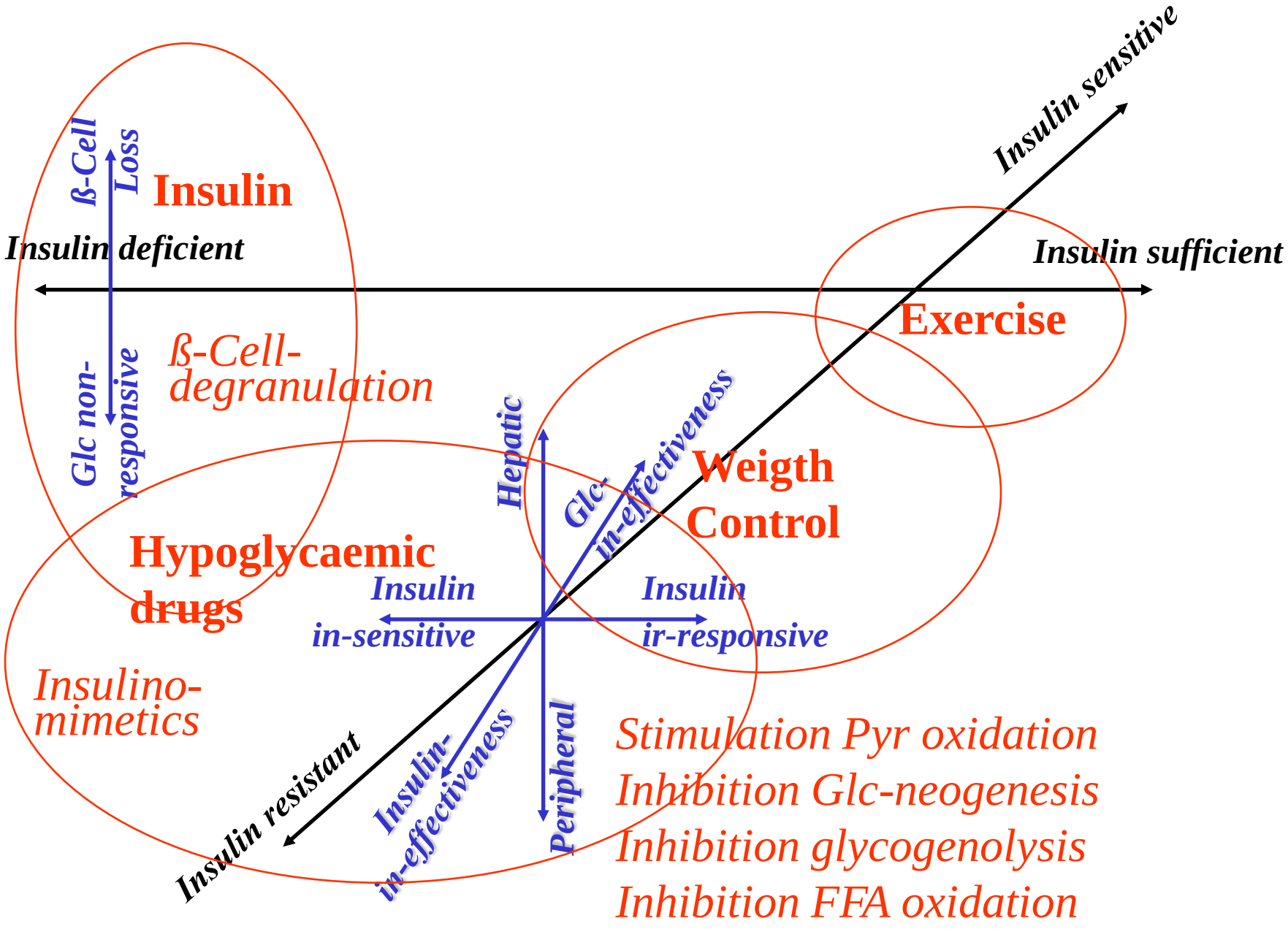
Diabetes Mellitus: Pathophysiological Staging 1/2



Diabetes Mellitus: Pathophysiological Staging 2/2

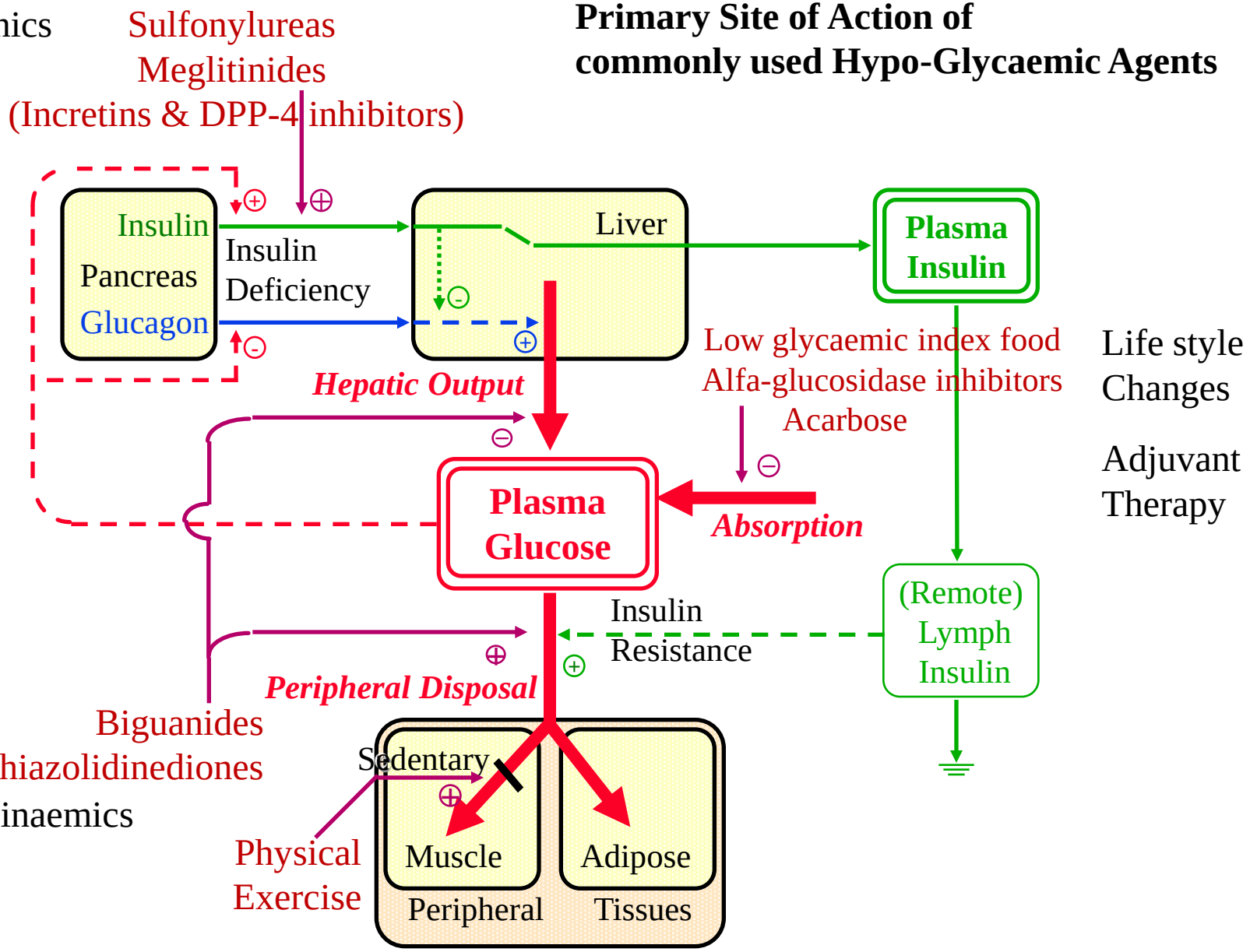


Diabetes Mellitus: Therapeutic Interventions



First-Line Treatment of NIDDM
Primary Site of Action of
commonly used Hypo-Glycaemic Agents

Non-obese
Insulinopenics



Life style
Changes

Adjuvant
Therapy

Obese
Hyperinsulinaemics

Do Clamp and Tolerance Protocols address Relevant Questions?

Pathology Staging & Therapeutic Interventions

Clamping Patients

Tight Control of Euglycaemia in Critically Ill Patients

= Clamp **= Euglycaemic** **= Insulin Resistant**

excess of counter regulatory hormones

= Hyperinsulinaemic

= Euglycaemic Hyperinsulinaemic Clamp

Insulin Action

tips Anabolic / Catabolic Balance

lowers Glycemia

Van den Berghe G *et al.*
N Engl J Med. **345**:1359-67 (2001)