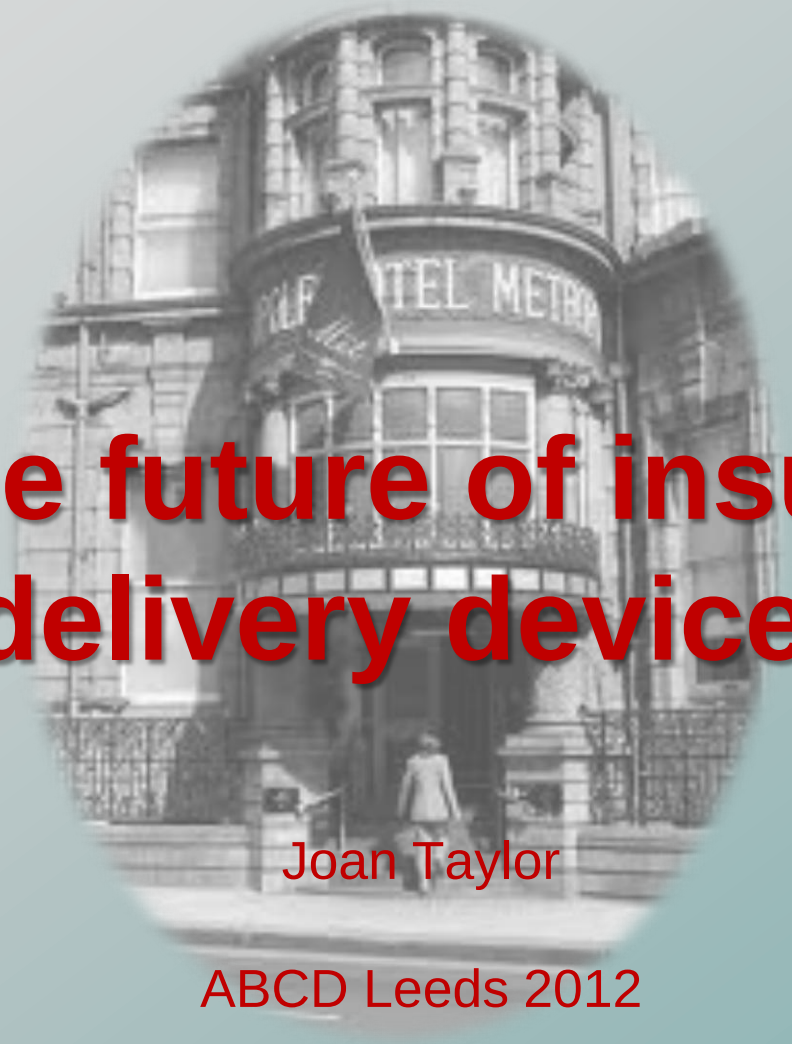


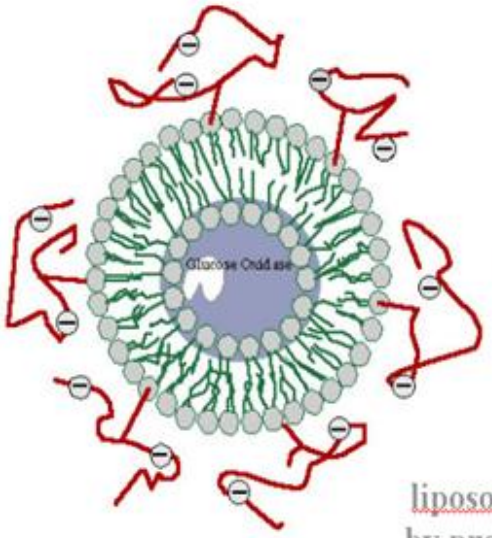
The future of insulin delivery devices

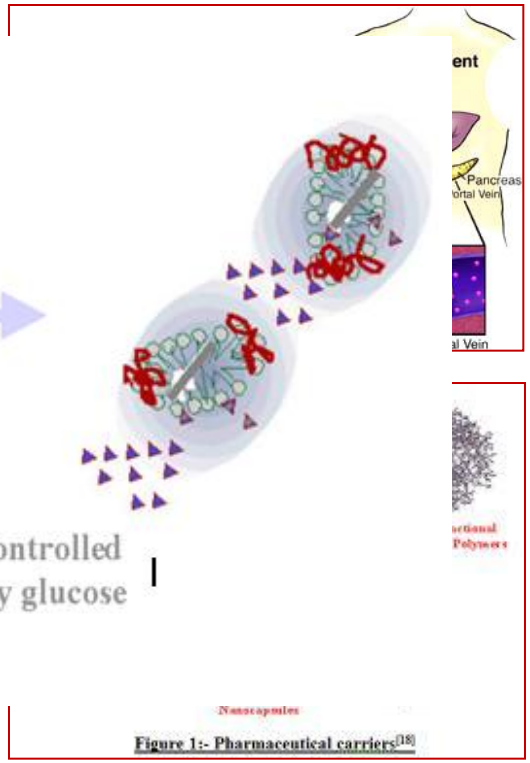
Joan Taylor

ABCD Leeds 2012

the remit does not include:

- be
  rep
- mi
  remedies

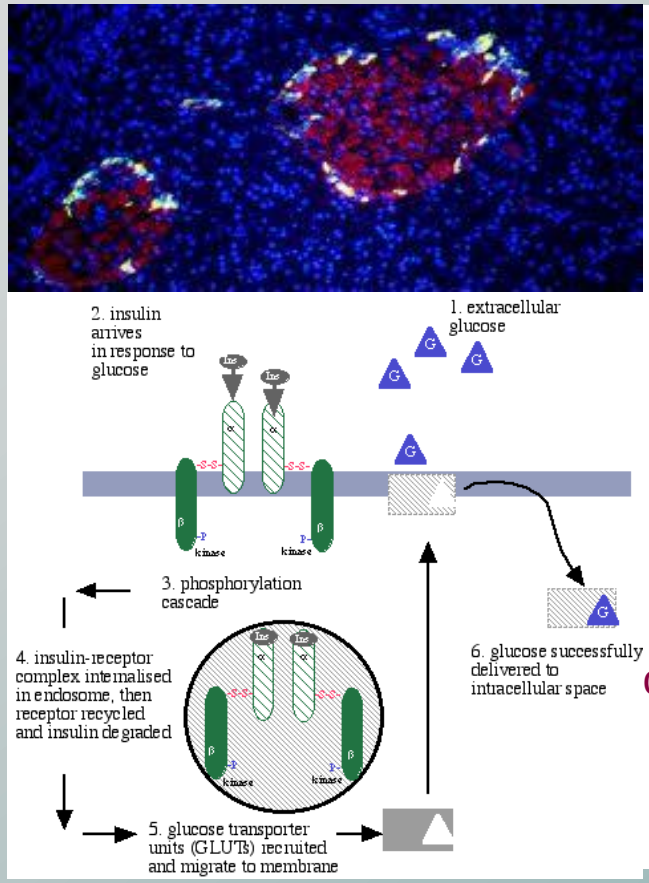




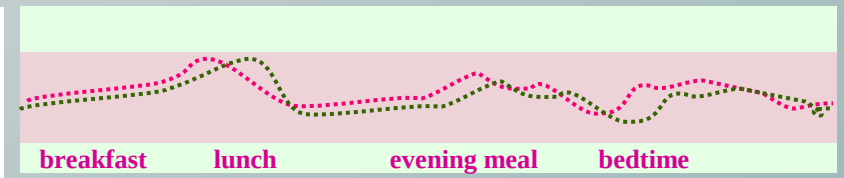
my focus

- the problem
- the insulins
- sensors
- pumps
- sensor assisted
- closed loop
- our results

diabetes

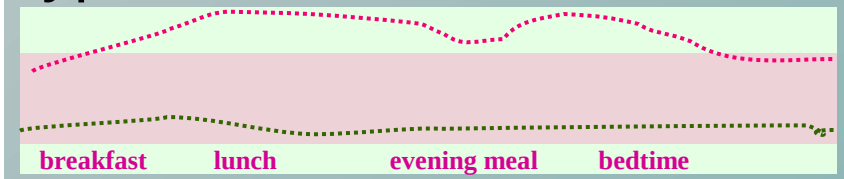


normal

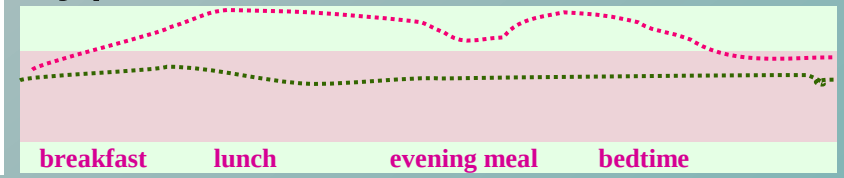


glucose
insulin

type 1



type 2

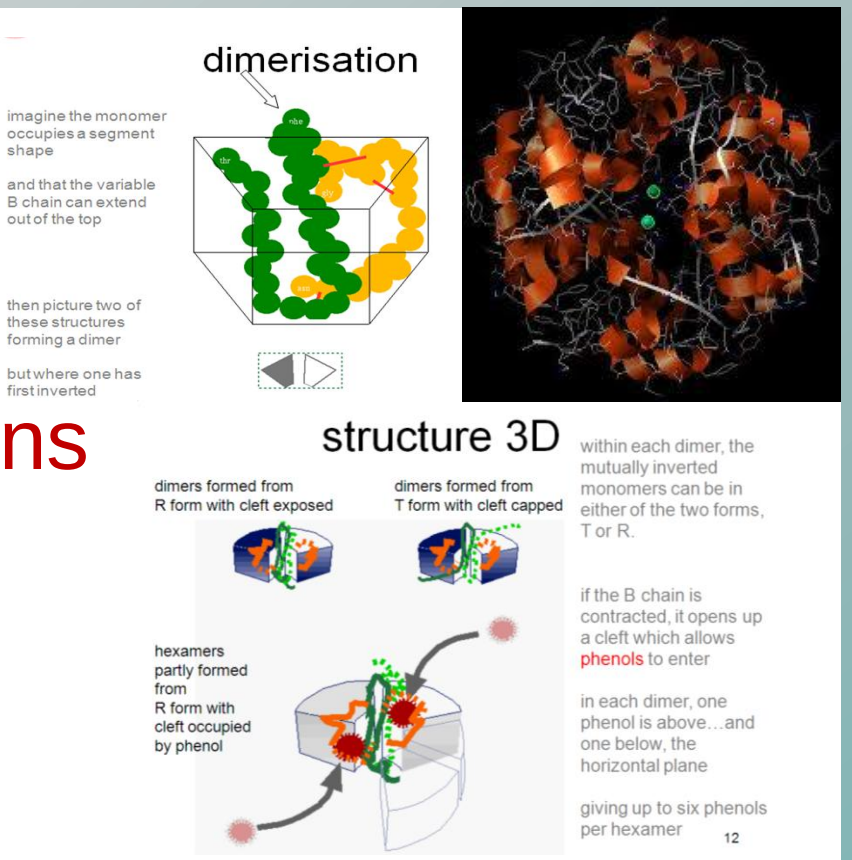


the status quo

- we understand much more
  - for example…….
- insulins have become:
  - purer
  - genetically engineered to become human
  - synthetically altered for different kinetics
    - lispro, aspart, glulisine
    - detimir, glargine (but only for subcutaneous)
  - solutions –no sedimentation or precipitation

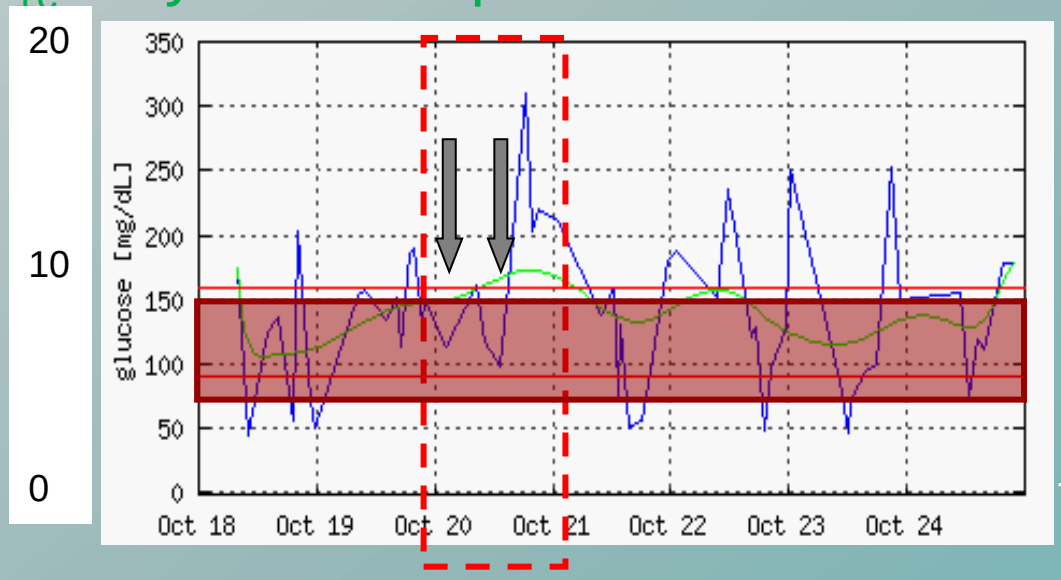
insulins

- phenol complexes
- hexameric
- monomeric
- smarter formulations
  - Viaject
  - Genapol



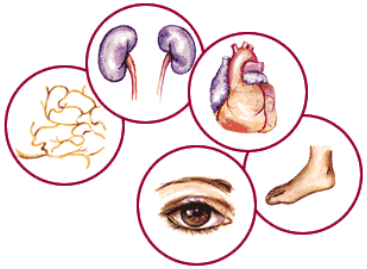
what's wrong with that? barriers to compliance

- may be well out of control some of each day –**cumulative** toxic mechanisms
- they may not pick this up when testing (peak 16mmol/L)
- means and HbA_{1c} may miss the problem



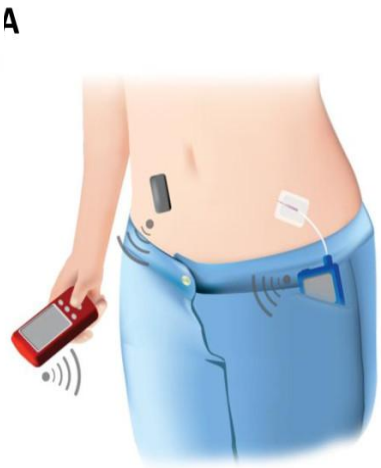
what's wrong with that? the complications

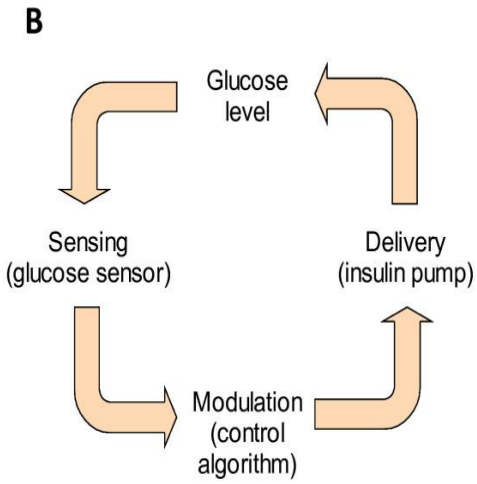
- damage from chronic high glucose (type 1 & 2)
  - **macrovascular**
    - stroke and heart attack
    - addressed with statins, aspirin and ACE inhibitors
    - however, **glucose** is likely to be the **underlying cause**
  - **microvascular** (obvious after 20 years)
    - kidney failure
    - amputations
    - blindness
    - minimised with good **glucose control**
  - nerve damage*



meters & sensors

- two major purposes
  - sensors have been important for **open loop** decisions
  - will be implicit for most **closed loop**

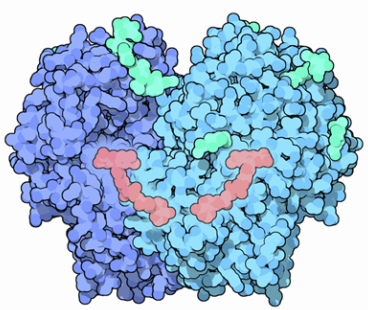


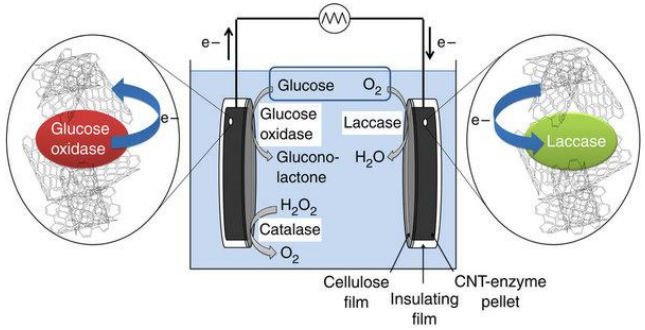


Hovorka

sensor chemistry & problems

redox cycles





- glucose oxidase has been a mainstay of testing for many years
- the oxidation cycle, working with other electron acceptor-donors generates a current
- sensor difficulties being solved **for indwelling**
  - protein and fibroblast deposition
  - embolism
  - calibration drift (needs clamp)
  - interference - paracetamol and vit C
  - temperature dependence
  - low oxygen tension
  - peroxide build up
  - **delays**

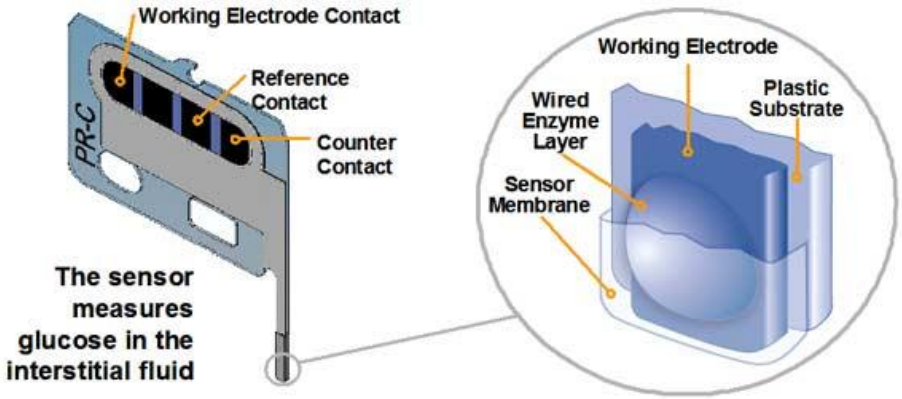
sensor innovation

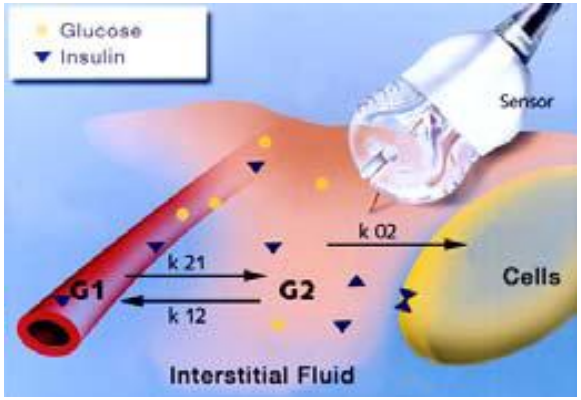
- for open loop testing
  - USB connections for PC transfer

  - sensor integrated with Smart phones

continuous monitoring

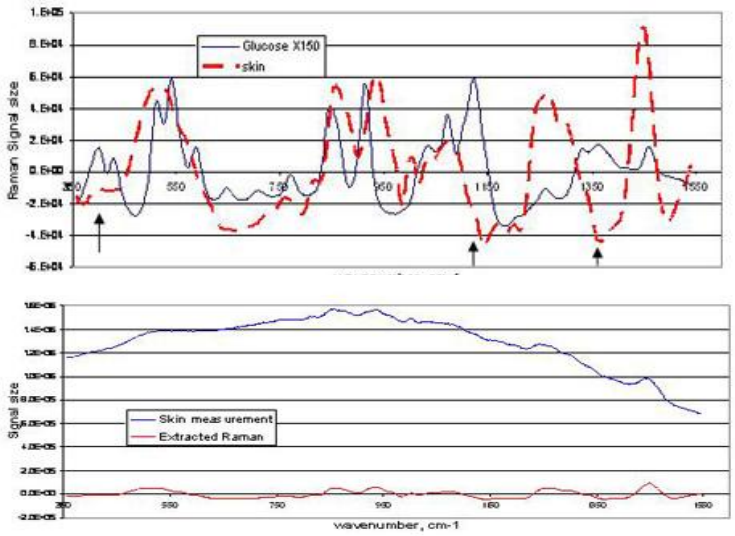
- interstitial fluid –indwelling (open & closed loop)
- electrochemically similar
- equilibration delays -more later

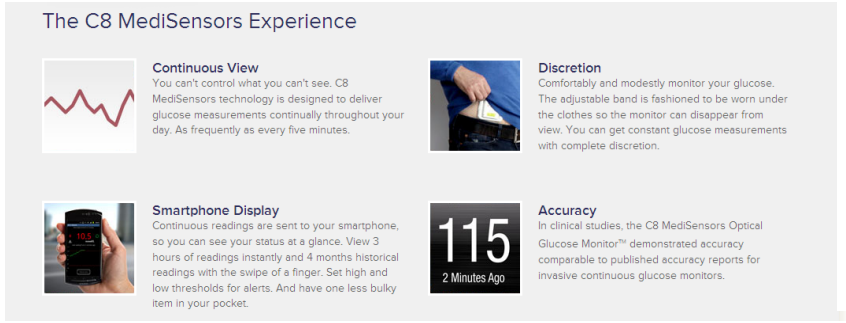




sensor progression

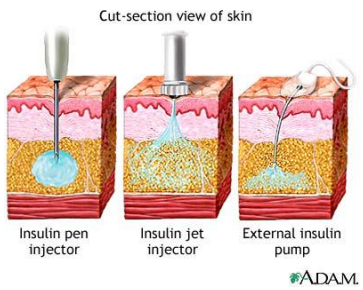
- non-invasive, in situ sensing (Raman IR)





pumps

- pumps were developed from the 1970s
- 1st order by injection, zero order by pump
  - gives better control than injections
  - fewer hypos and better HbA1c values
  - few unintentional peaks/troughs in output from site



pumps

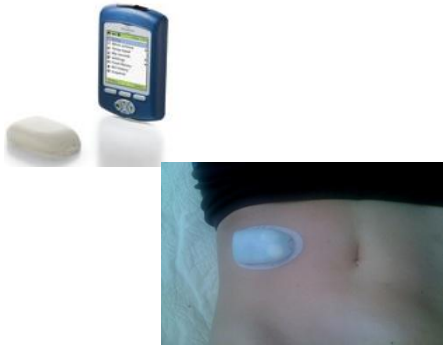
- highly developed
- stand alone
  - Animas Lifescan
  - Accu-Chek Spirit
  - Medtronic Veo
  - touch screen types (Tanc
- barriers to success

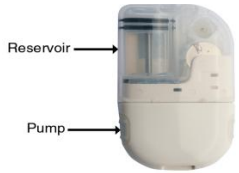
patch pumps

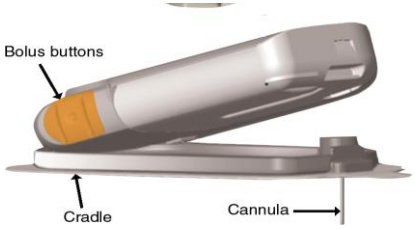
- connects with very short tube at the back
- seems more acceptable

patch pumps

- some examples
  - Omnipod –the first, waterproof, type 1 and 2
  - Solo –longer shelf life on skin, not waterproof, still needs filling often per week (Mendingo –Roche)
  - CeQur (Boston) –type 2 but not yet marketed





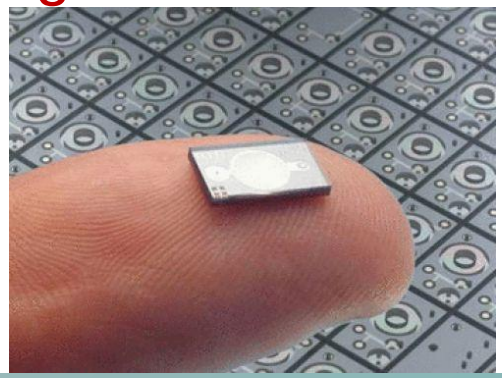


patch pumps

- Cellnovo -touch screen, data logging and cloud technology

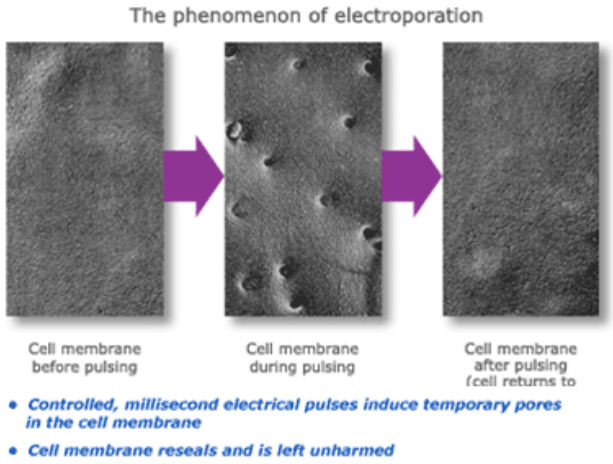
patch pumps

- Micropump Debiotech Jewel
- dimension ratio
  - makes device smaller and more acceptable
  - pump action –low shear, spares insulin
  - minute mechanism leaves large reservoir room



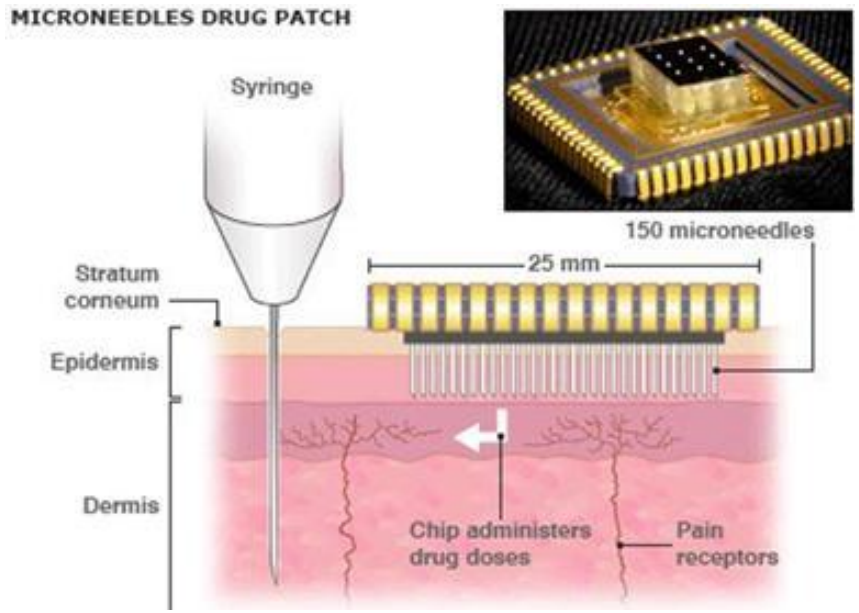
patch pumps

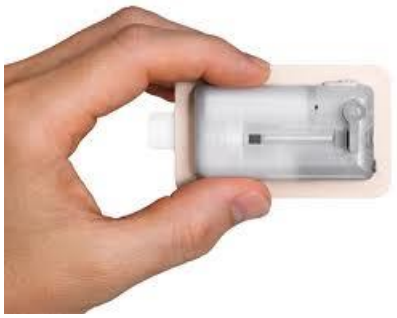
- Altea –the electroporation Passport
  - needle and cannula-free
  - delivery local or means to systemic
  - may now be defunct

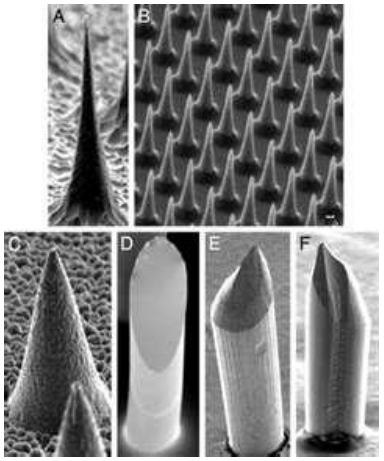


patch pumps

- microneedle technology
  - Valeritas V-Go



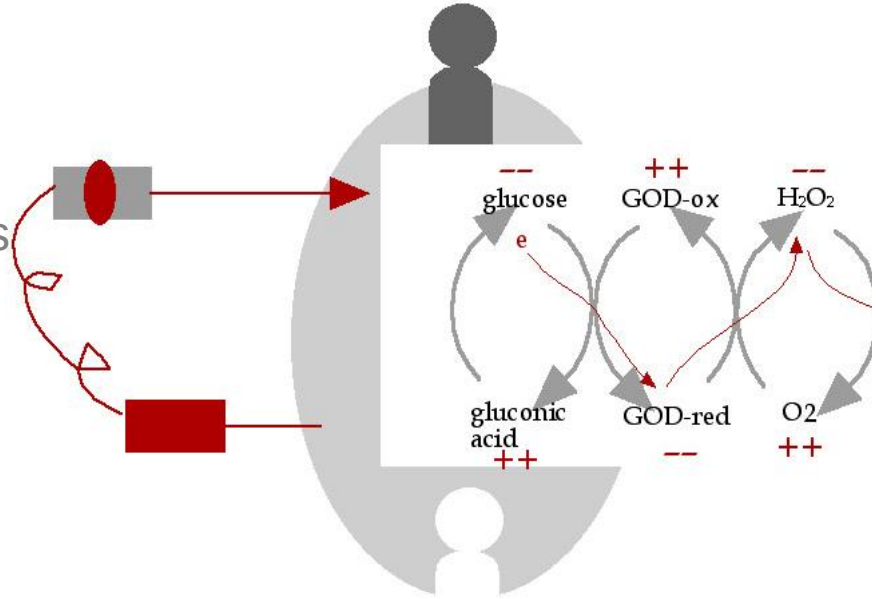




integrated sensor and pump

more about direct contact sensor problems

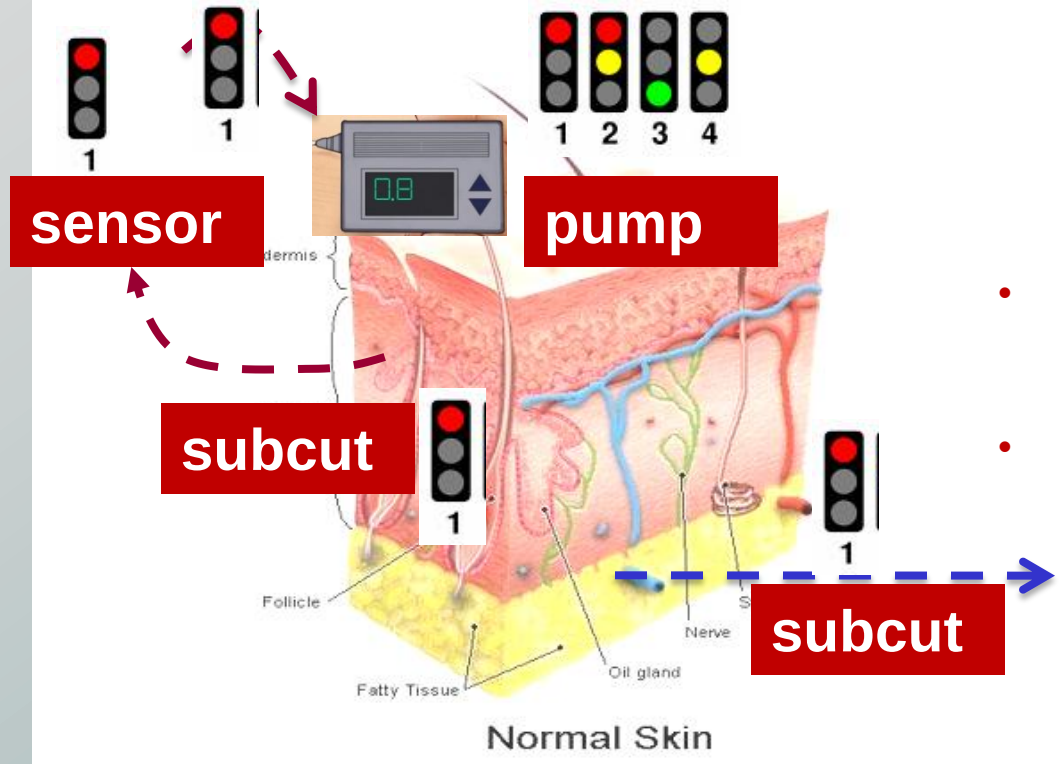
microprocessor controlled pumps linked to electronic glucose sensors



sensor difficulties being solved for indwelling

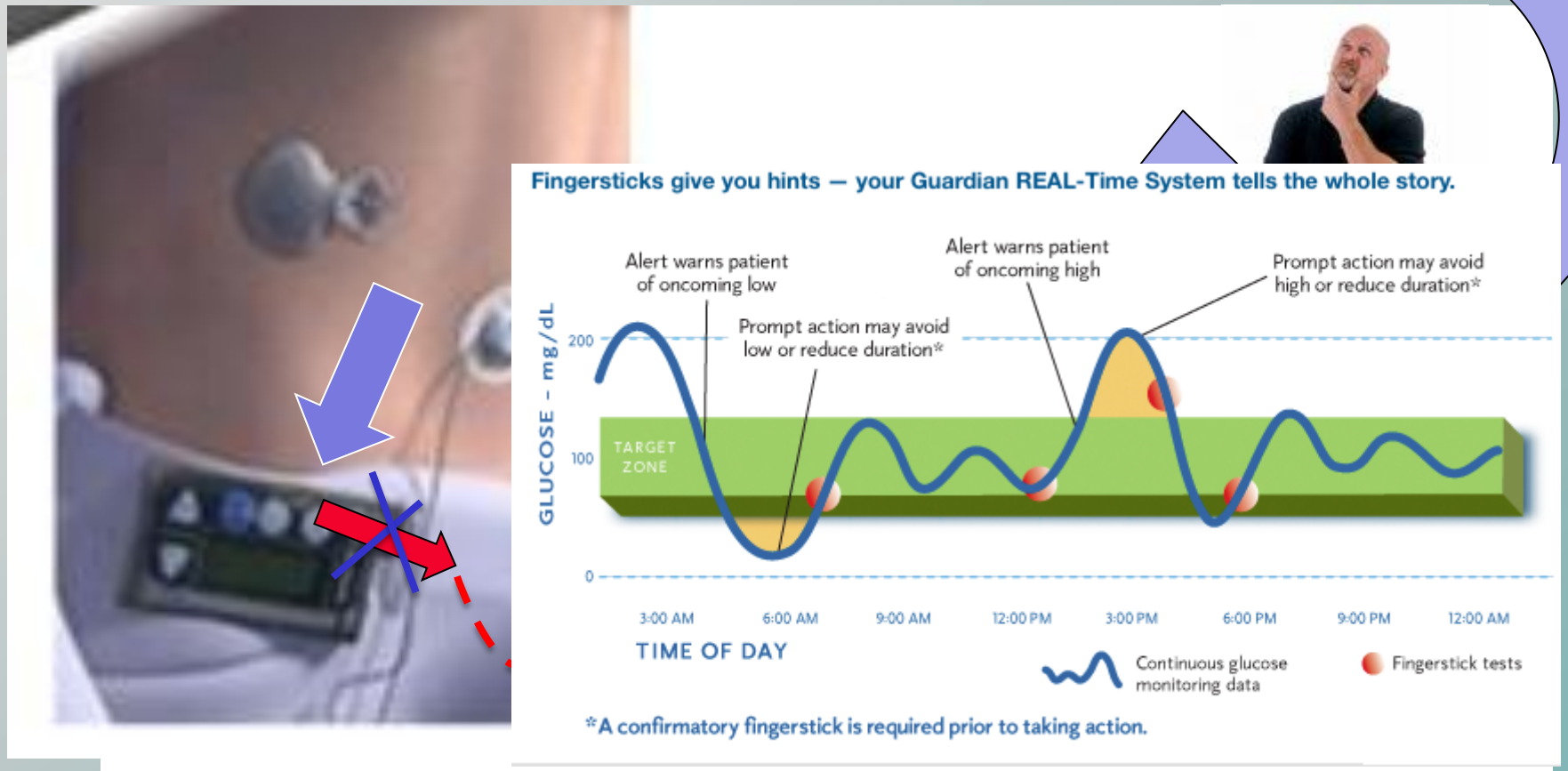
- protein and fibroblast deposition
- embolism
- calibration drift (needs clamp)
- interference - paracetamol and vit C
- temperature dependence
- low oxygen tension
- peroxide build up
- **delays**

subcutaneous delay



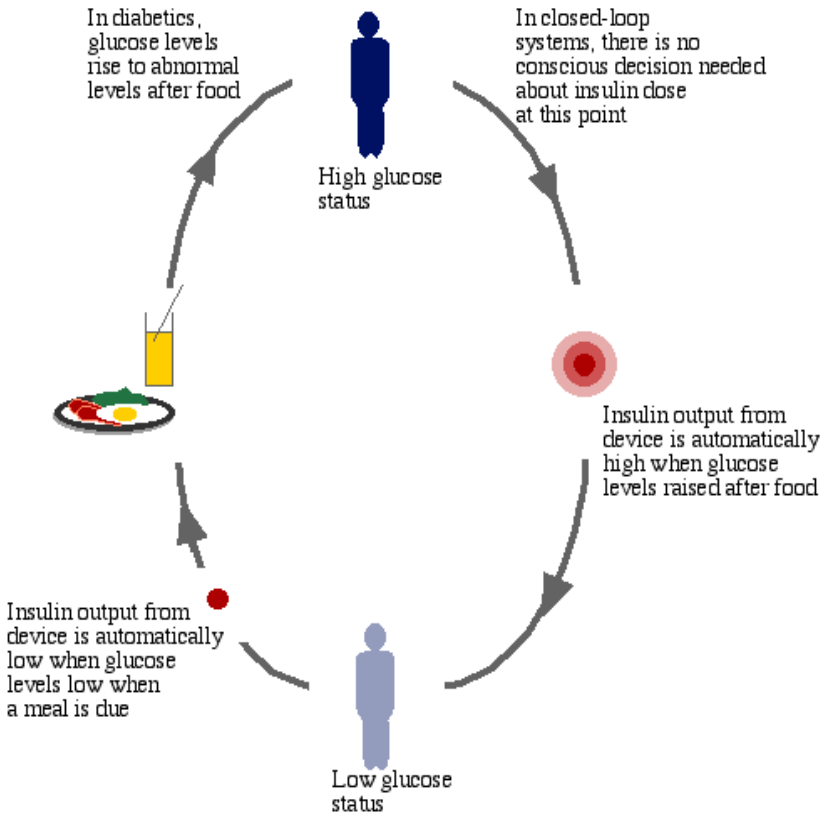
- time lags
  - blood to interstitial fluid
  - sensor uptake (diffusion)
  - response due to compensatory filters
  - insulin release to plasma
- complex algorithms needed
  - timely (compensate for lags)
  - biphasic as for normal
- heating, vibration, hyaluronidase

loop is still mainly open



closed loop control

- a need for:
  - continuous delivery
  - constant feedback
  - auto real time adjustment

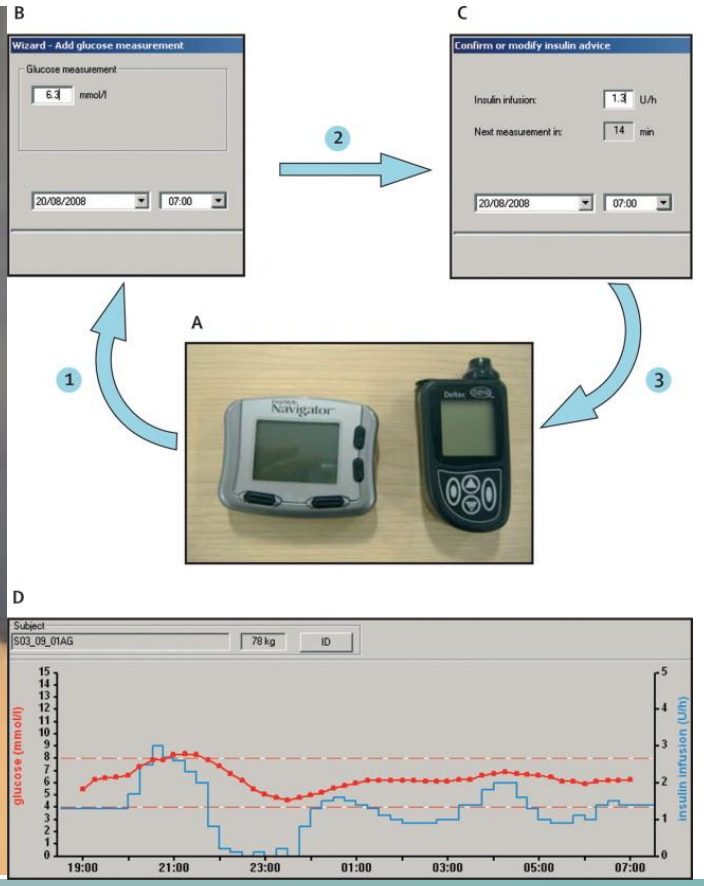


the requirements

- be specific for glucose
- switched on by high glucose
- curtailed by low glucose
- respond in correct time-scale
- able to transmit the variable rate in real time to plasma
- respond in dose-related manner
- detailed control without undue oscillation
- deal with *local visceral* insulin and glucose levels not *skin*
- not produce increased need (“down regulation”)
- avoid leak of dose or components or other harm
- deliver unmodified insulin (other than monomeric)
- operate long term

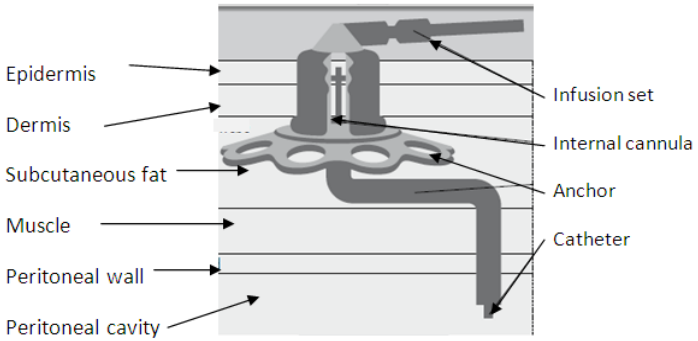
the Cambridge approach

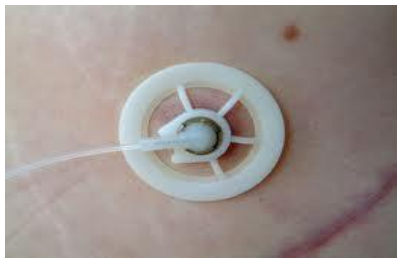
- gr
  -
  -
  -

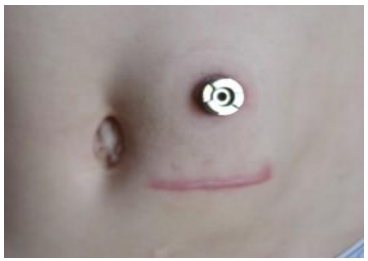


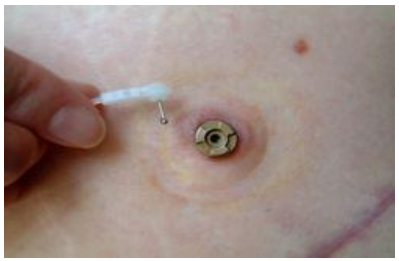
the Diaport

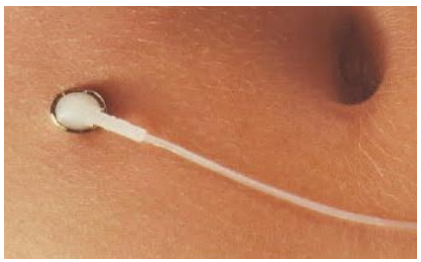
- peritoneal delivery by external infusion



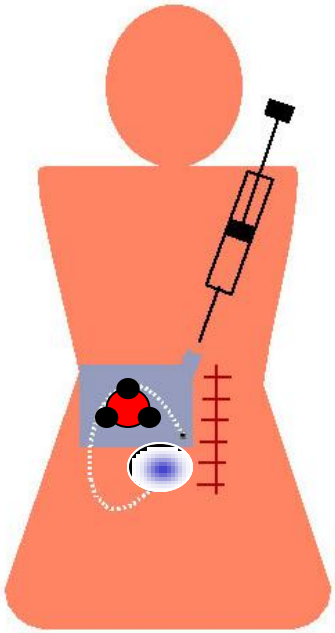








totally implantable pump



- at first was mainly programmable

- refillable

- has now been adapted to closed loop with an implanted sensor coupled to a microprocessor vascular & subcutaneous sensors trialled

totally implantable pump

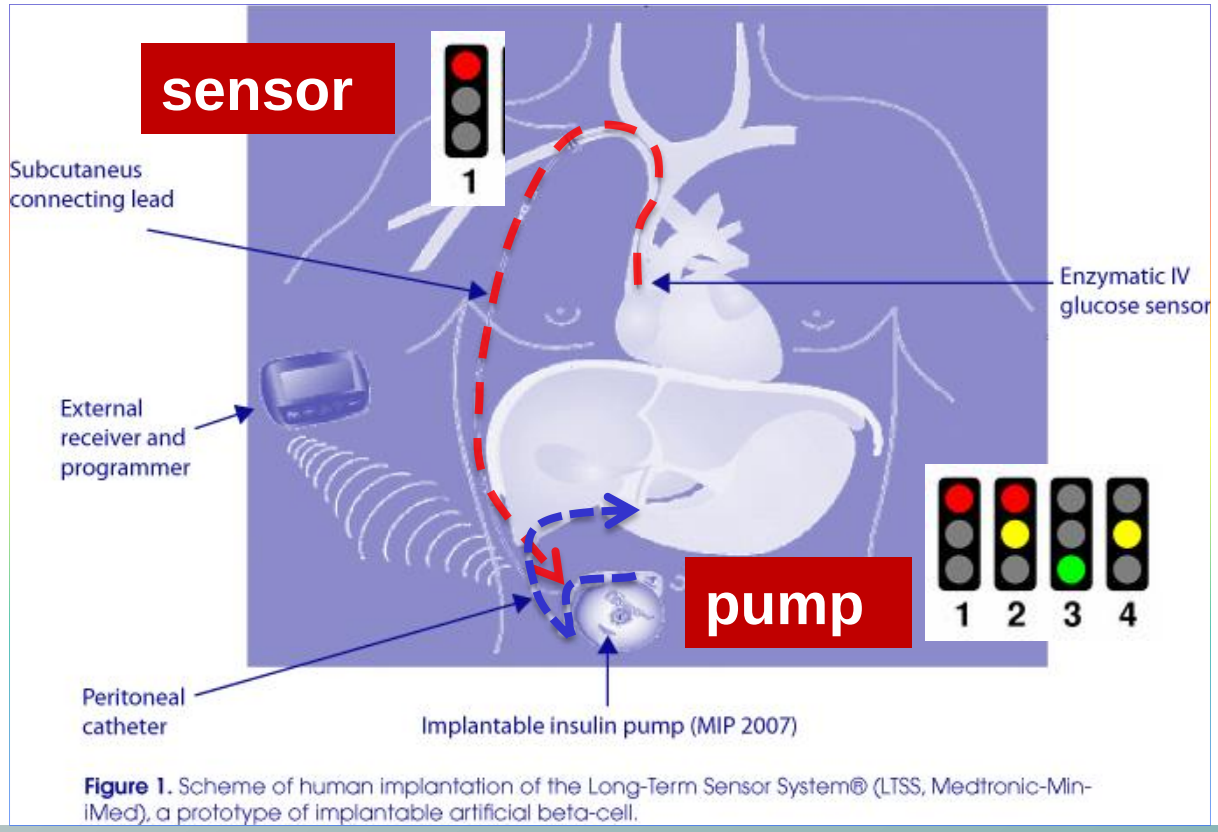
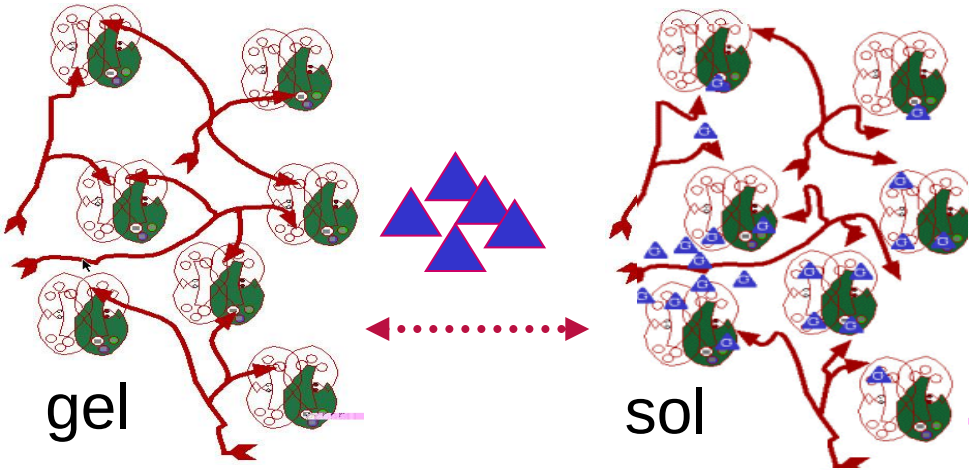
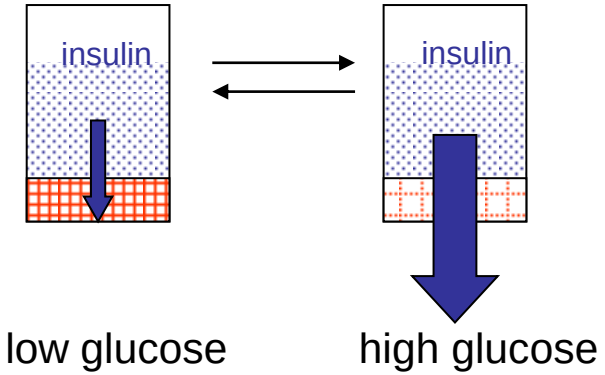


Figure 1. Scheme of human implantation of the Long-Term Sensor System® (LTSS, Medtronic-MiniMed), a prototype of implantable artificial beta-cell.

our technology

- device with glucose sensitive gel
  - governs output from insulin depot

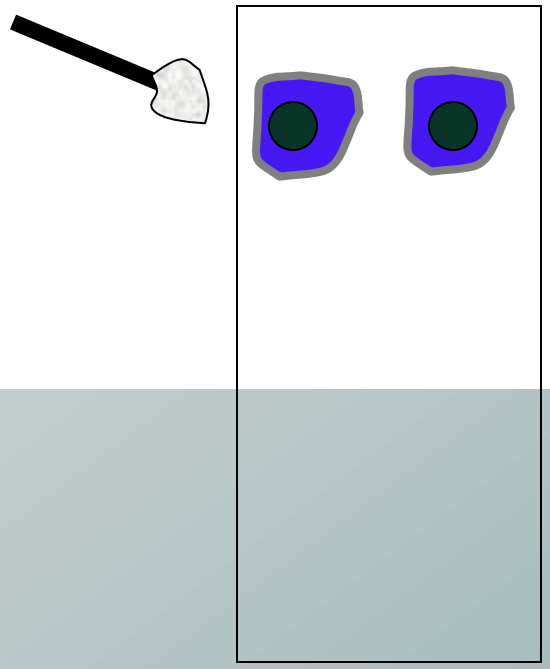




  - insulin travels out faster when glucose softens gel
  - reverses when glucose level falls
  - it is a closed loop system

our technology

how the gel responds to glucose



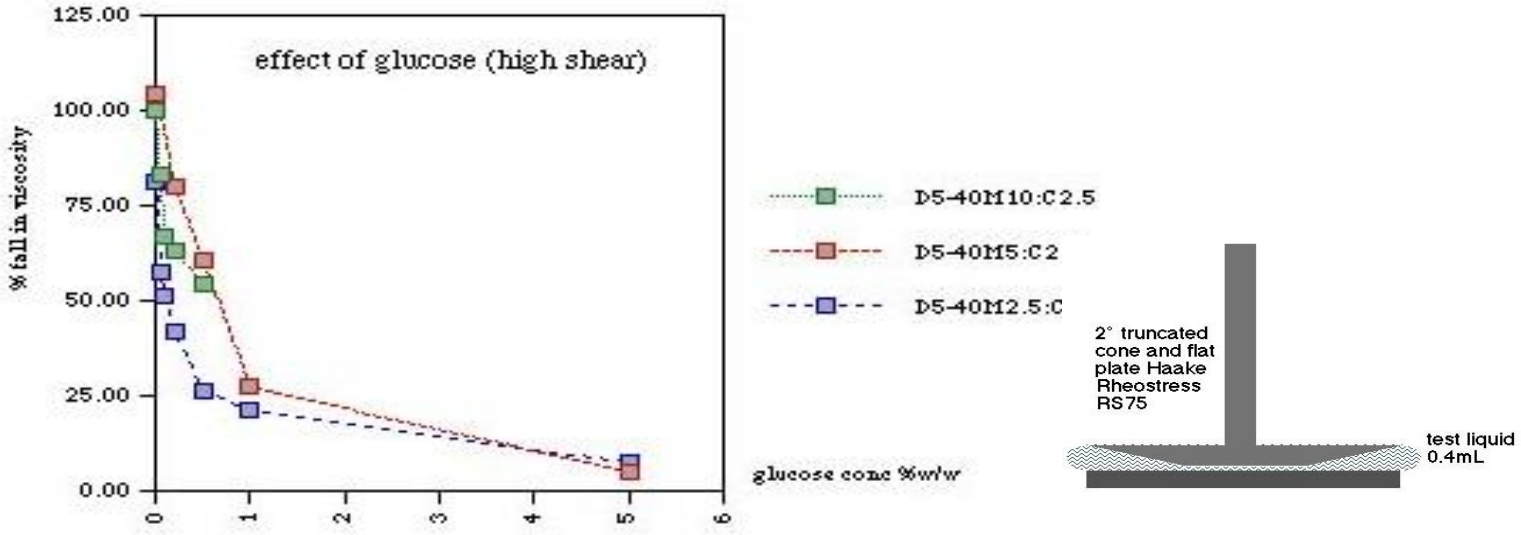
steel balls

stuck on gel samples on glass slide

dry glucose added

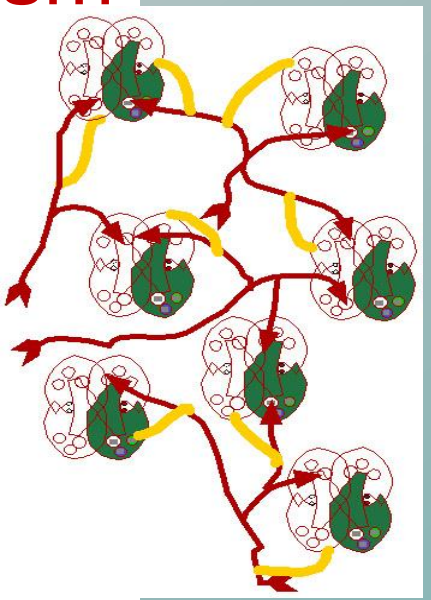
our technology

- in vitro evidence
  - measuring the viscosity changes
    - using standard methods
    - viscosity falls over relevant values



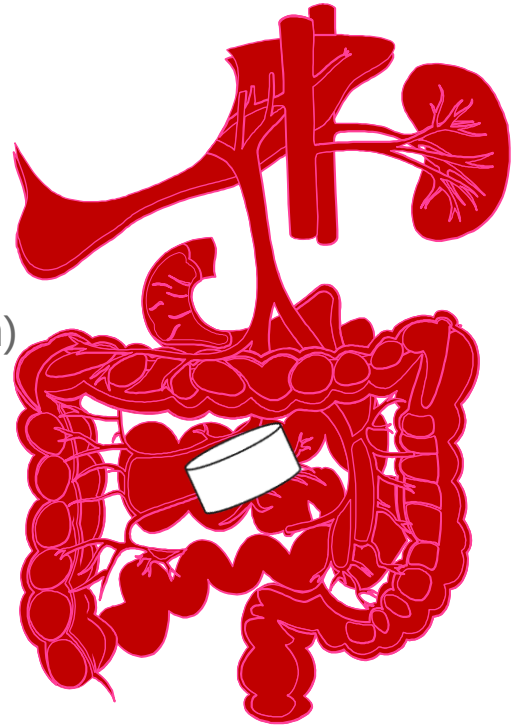
our technology

- improving the basic mechanism
  - component movement
    - loss and phase separation
      - could disable mechanism
      - could be toxic
  - remedies
    - bond molecules together
    - standard covalent bonding & polymerisation
    - small pore size



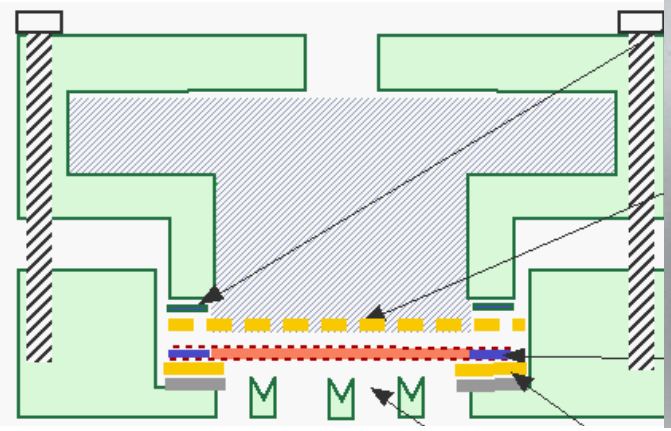
the peritoneal site

- allows sensing of ambient glucose
  - glucose equilibrium blood:peritoneal fluid
  - delivery is always appropriate
- allows delivery directly to liver
  - small aliquots
  - fast, not rate-determining
    - mesenteric veins drain peritoneum (cf skin)
    - mesenteric to portal to liver route
- metabolism of dose is rapid
  - no hypos
- but clearly invasive and difficult



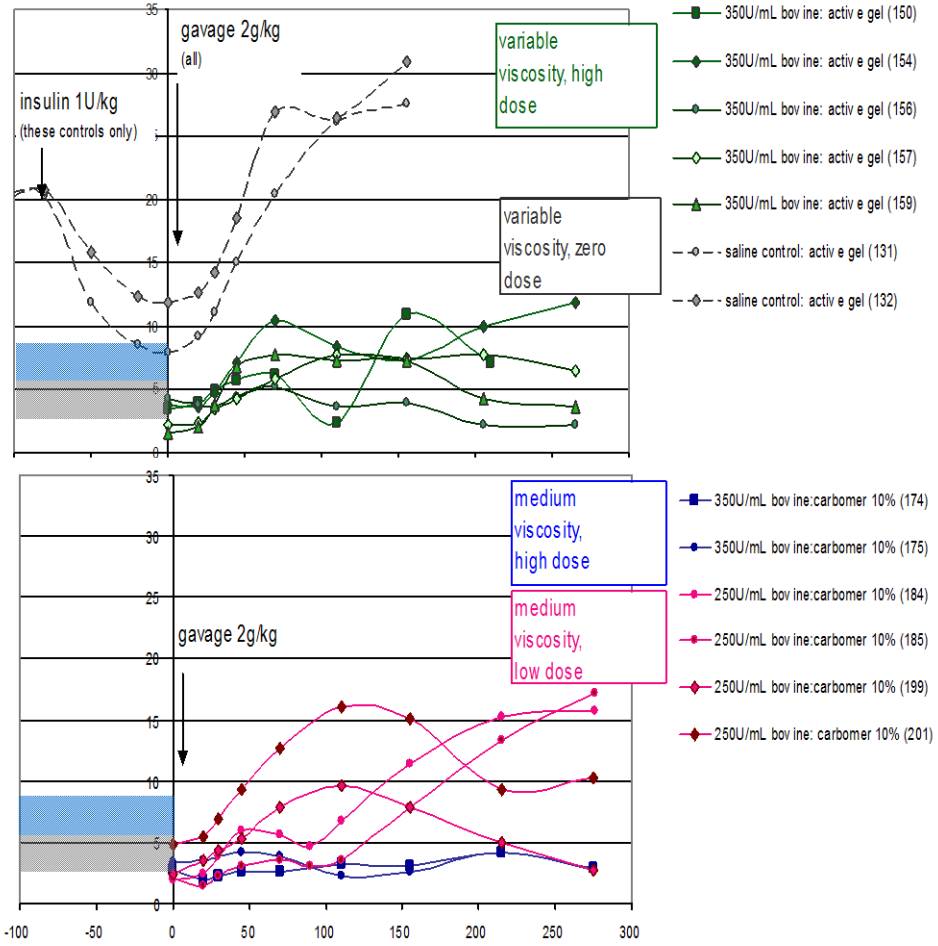
rat trials device

- testing the feedback
  - building simple in vivo test cell
  - for peritoneal implant

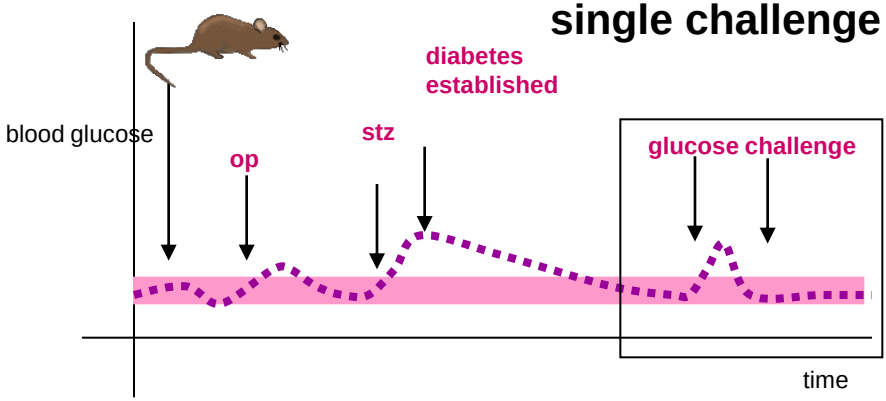


rat trials

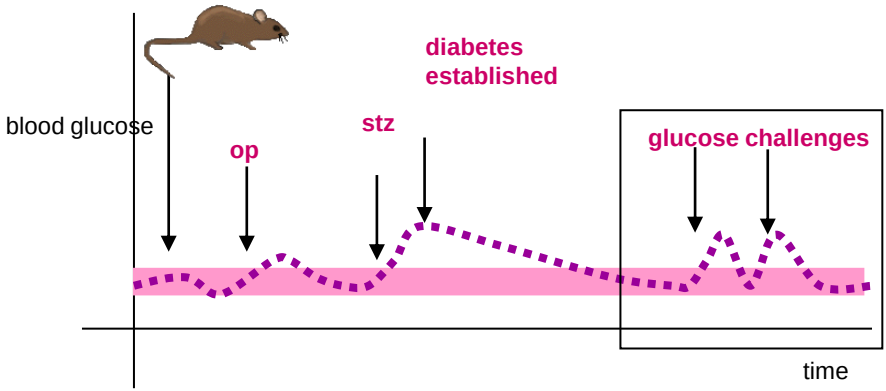
- initial single challenge *in vivo* results -worked well



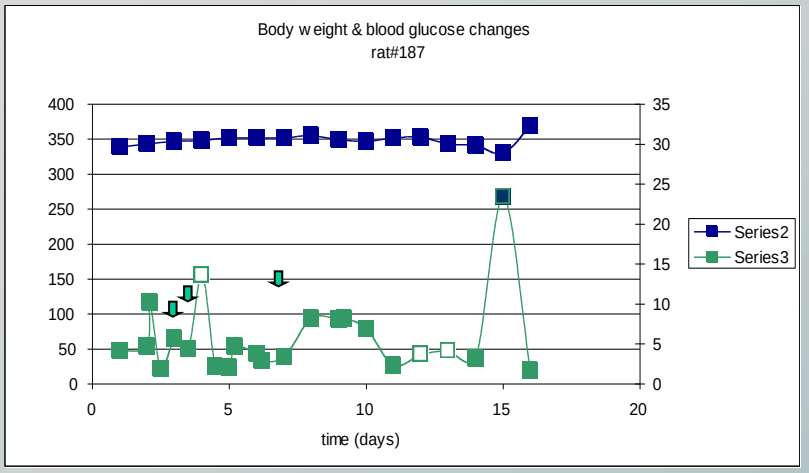
single challenge

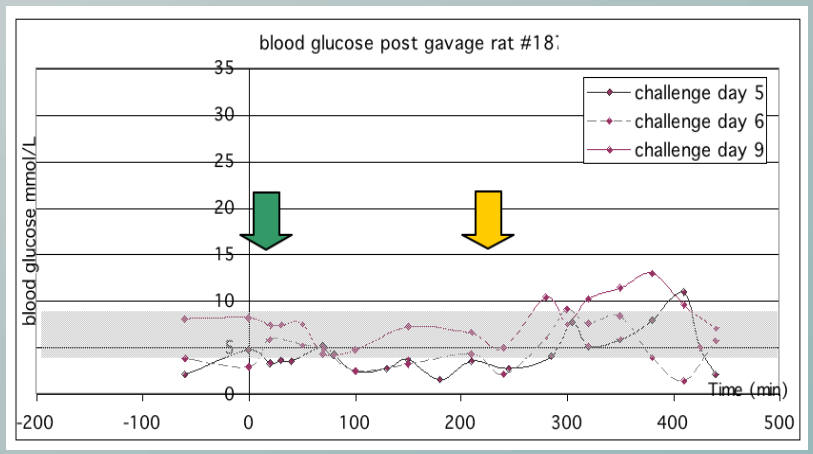


needed to prove multi-challenge



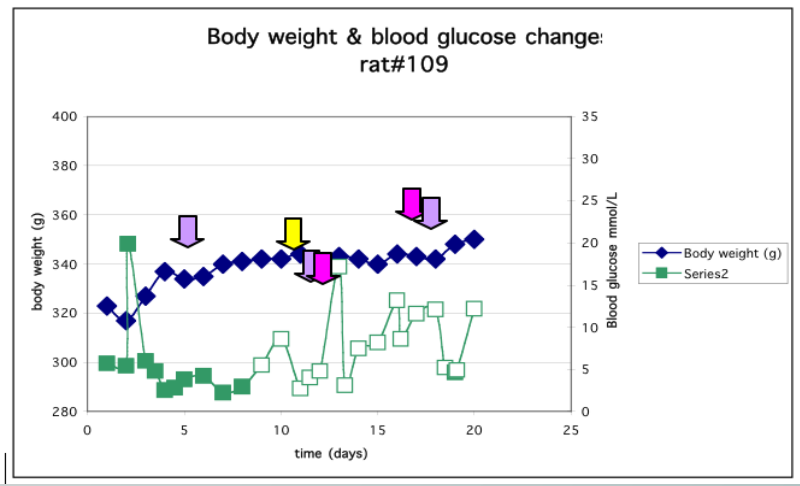
multi-challenge tests

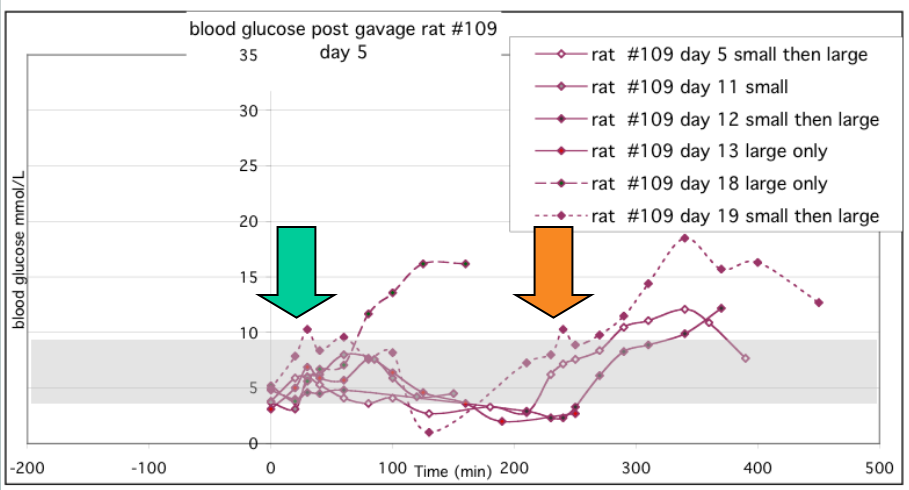




- method development has lead to longer working times
- allowing multi-challenge (feasibility of long term use)
  - morning BG readings on the left (diabetes revealed here, incidentally)
  - three challenge days
  - each comprises a standard and a large challenge
  - all BGs remain in range each time

control experiments

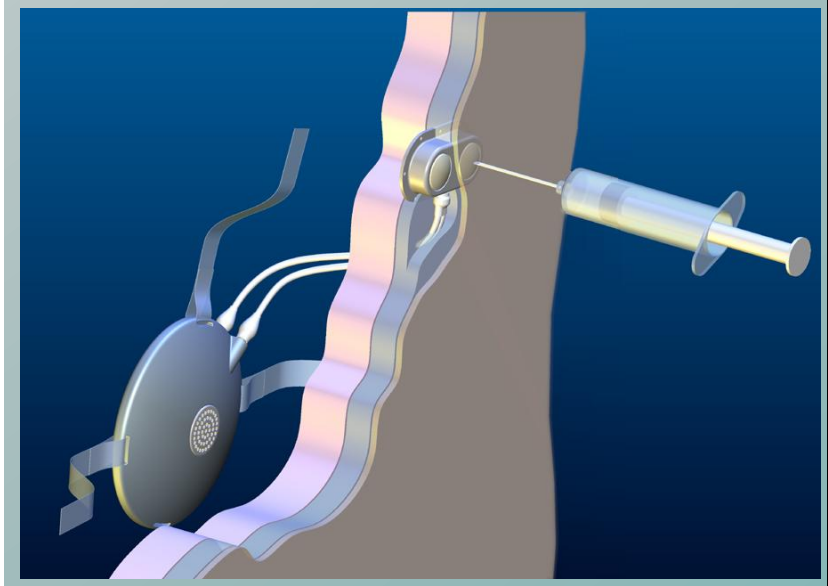




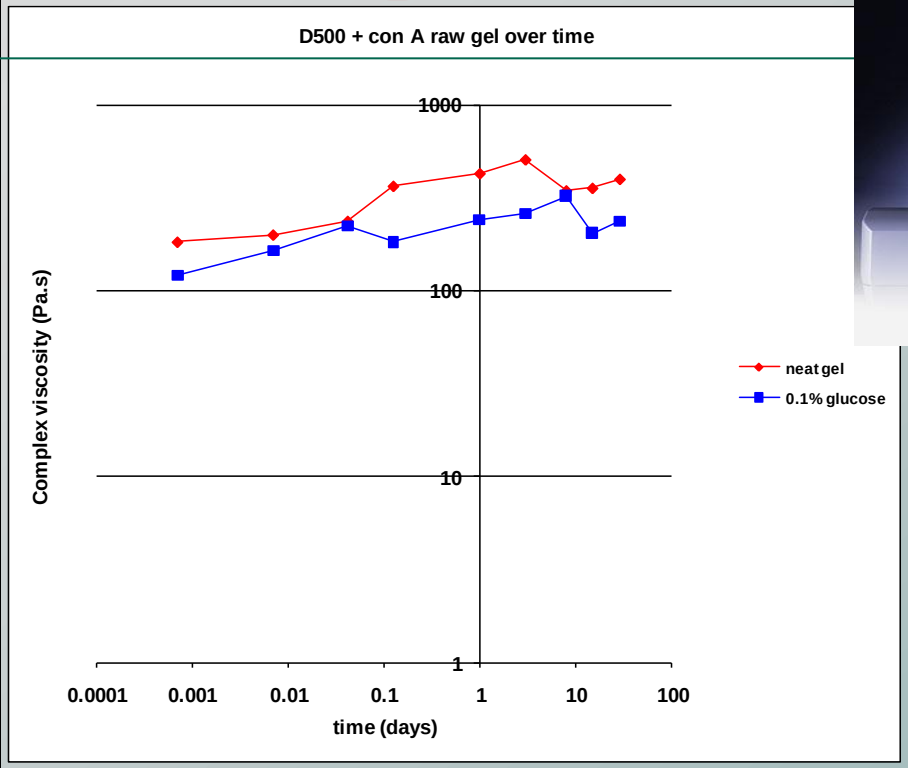
- successfully exposing failure of control experiments
  - also affected by calorie intake and output
    - but withholding food suppresses peaks
  - repeated challenges reveal lack of control
    - as seen here in this long lasting control experiment

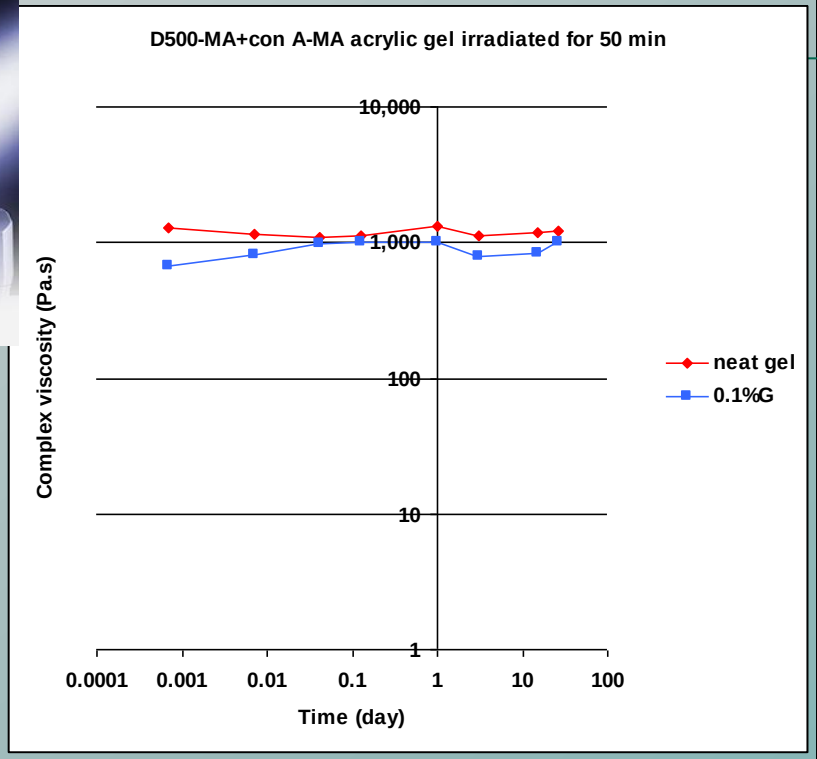
clinical design

- simple ‘closed loop’ pump
  - based on a chemical response
  - glucose-specific one-step response
  - responds rapidly and in therapeutic range
  - no biological, electronic or moving parts
  - needs no battery power
  - needs no immunosuppressive drugs
  - could be available in large numbers
  - could be cheap to produce
  - could be simple to implant
  - could be refillable



gel stability

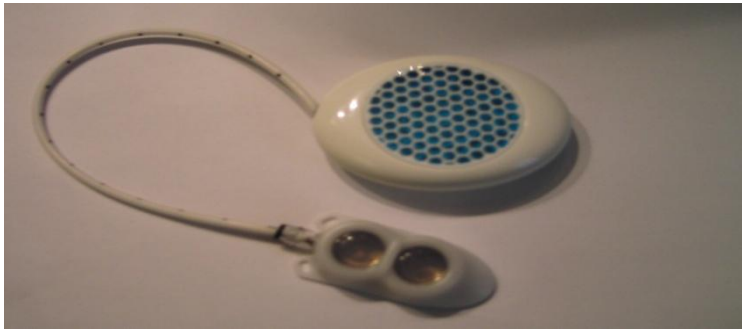




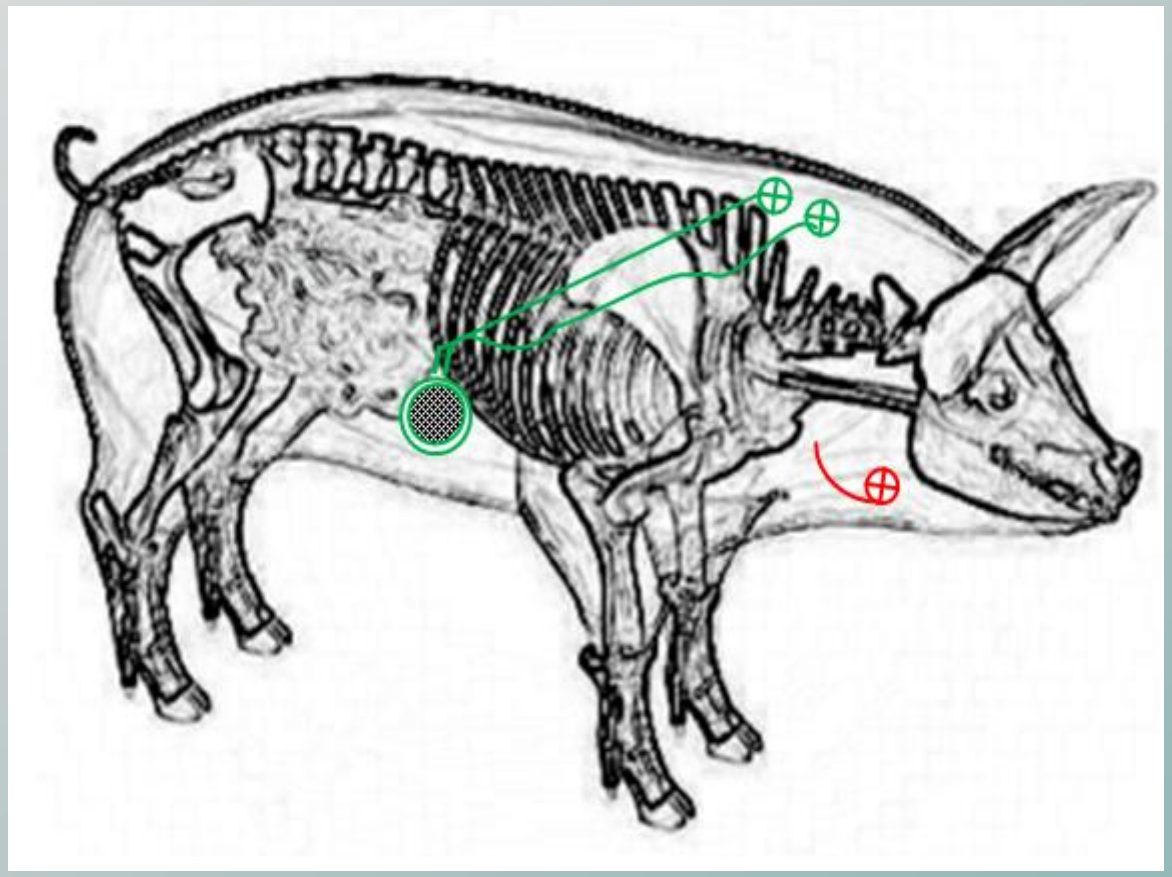
- method –dialysis bags
- creatinine (132mmol/L), lactic dehydrogenase147U/ml), albumin(21.2g/L), bilirubin (305mmol/L), triglycerides (0.7mmol/L), cholesterol (1.7mmol/L), glutamic oxalactic transaminase(40U/L)
- chymotrypsin could breakdown con A into peptides and amino acids

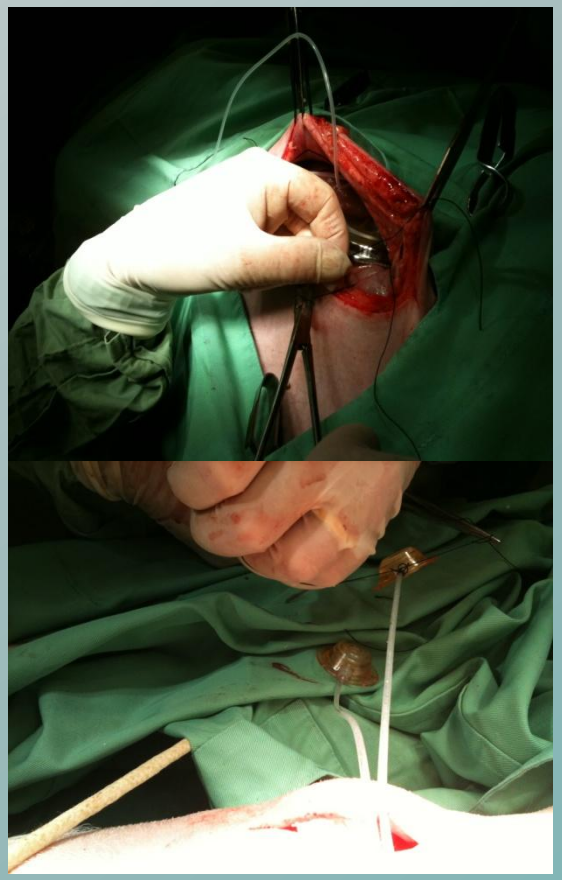
pig device & clinical maquette

- actual “works-like” prototype for trials in large animals
  - designed for repeated dismantling in trials so not pretty
- mock-up “looks-like” prototype
  - looks more like the clinical version
  - cartridges and minimised features



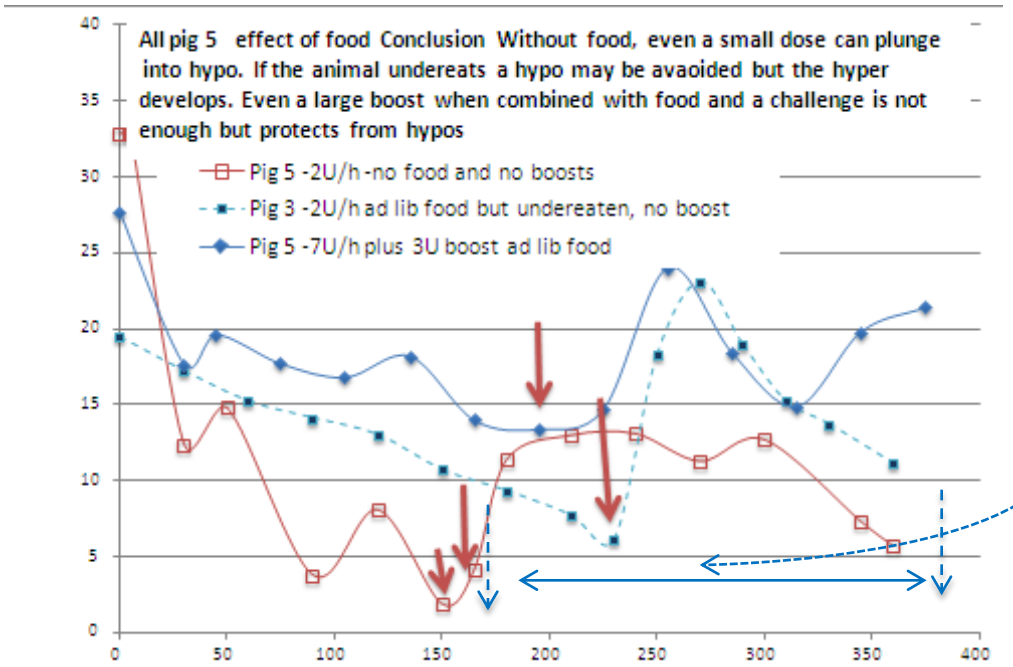
pig trials



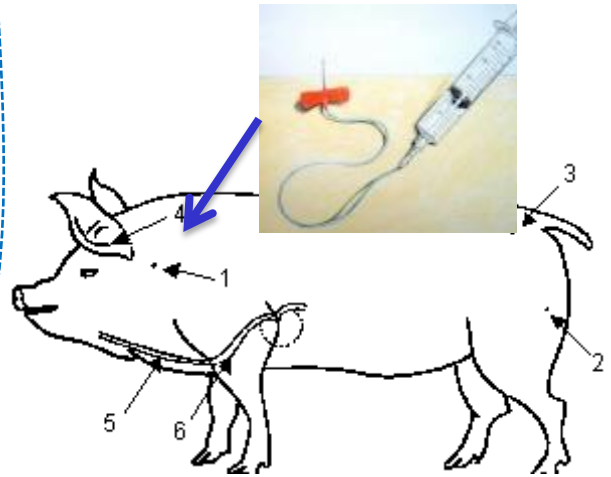


pig trials

iv calibration



hours well above normal

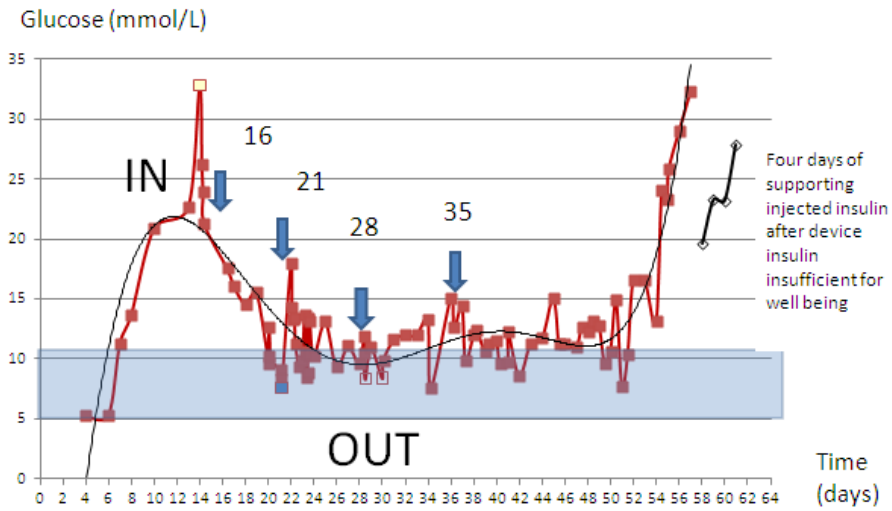


min

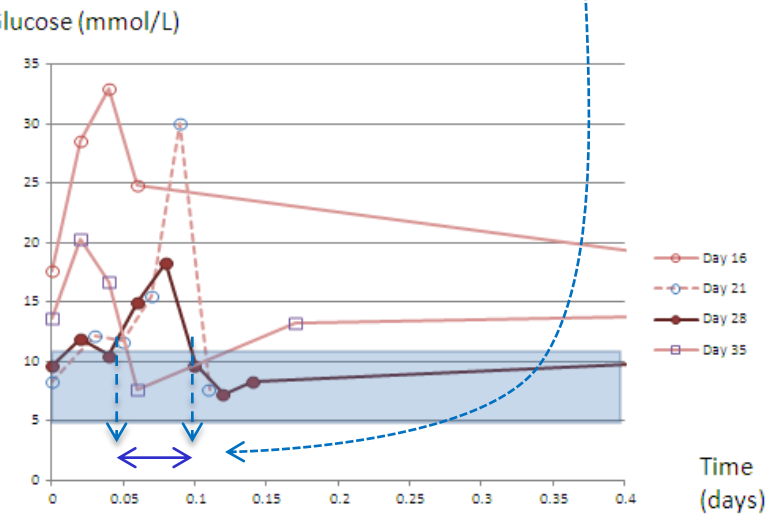
=0.27 days

pig trials

performance of the device



about one hour above normal



summary

- closed loop is the way forward
  - normalise life
  - optimise outcomes
  - relieve anxiety and illness
  - minimise treatment events
  - regularise glucose
  - reduce expenditure
- alternative methods
  - biological and electronic methods are not the only way