



The future of insulin delivery devices

Joan Taylor

ABCD Leeds 2012

the remit does not include:

The image is a composite of three parts. On the left, there is a photograph of a woman with curly hair speaking into a microphone. In the center, there is a scientific diagram showing a green spherical structure labeled "Glucose Oxidase" with red wavy lines extending from its surface. Below this is a purple arrow pointing to another diagram where the green sphere is shown with red fragments and purple triangles, with the text "liposome integrity controlled by proton released by glucose oxidation". On the right, there is a diagram of a blood vessel system with labels for "Pancreas", "Portal Vein", "Gastric Vein", and "Intravenous Polymers".

- be
rep
- mi
remedies

Nanocapsules
Figure 1:- Pharmaceutical carriers^[18]

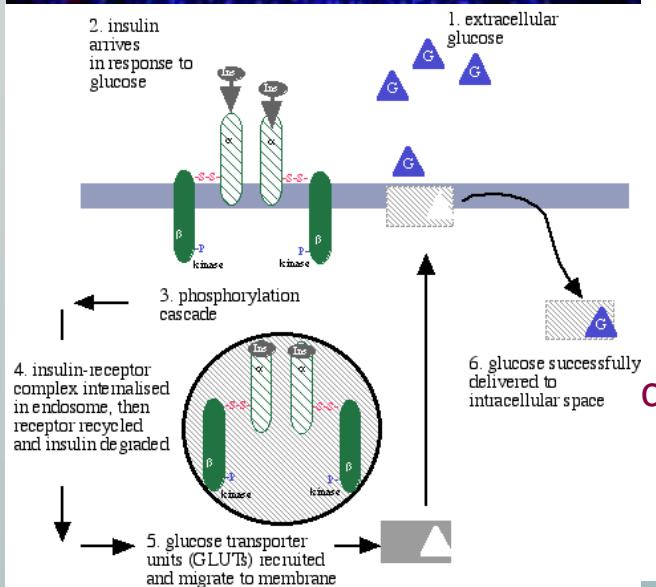
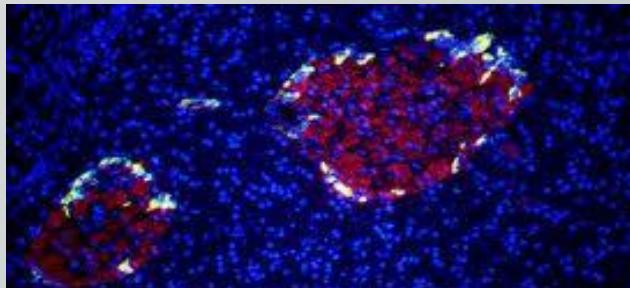


my focus



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

diabetes



normal



type 1



type 2





the status quo



ient J.L., December 15, 19

February 15, 1923

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

insulins

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

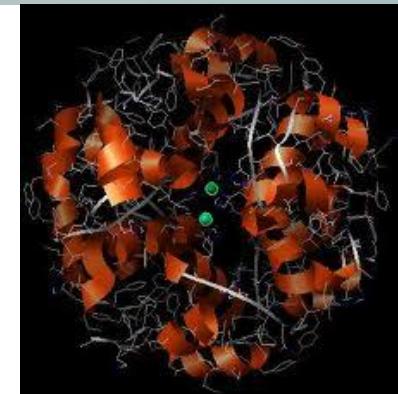
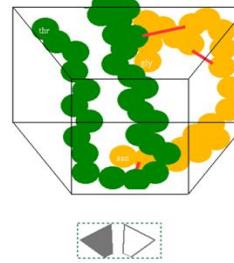
imagine the monomer occupies a segment shape

and that the variable B chain can extend out of the top

then picture two of these structures forming a dimer

but where one has first inverted

dimerisation



structure 3D

dimers formed from R form with cleft exposed

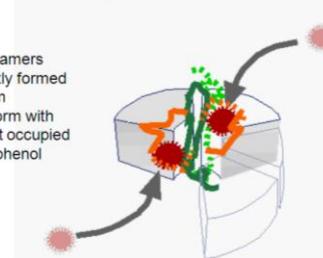


dimers formed from T form with cleft capped



within each dimer, the mutually inverted monomers can be in either of the two forms, T or R.

hexamers partly formed from R form with cleft occupied by phenol



if the B chain is contracted, it opens up a cleft which allows phenols to enter

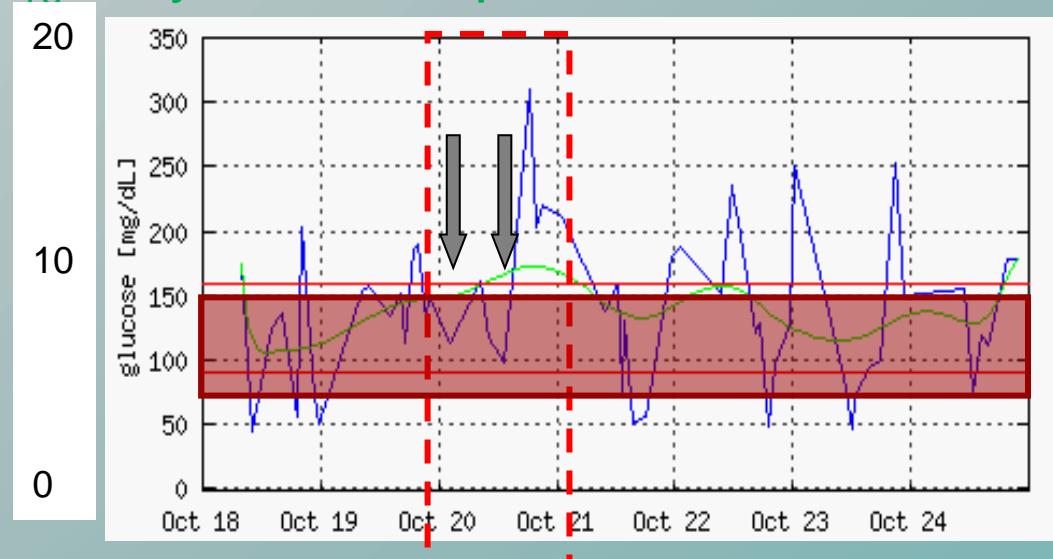
in each dimer, one phenol is above...and one below, the horizontal plane

giving up to six phenols per hexamer

12

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

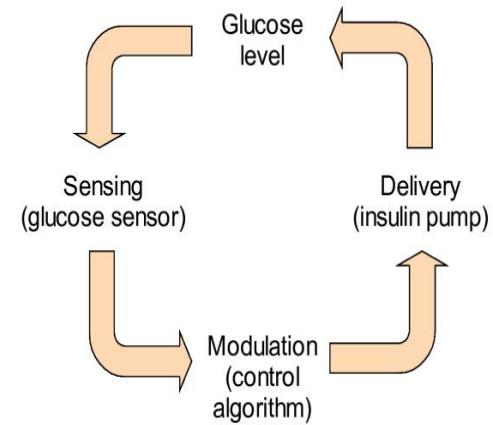
- sensors have been important for **open loop** decisions
- will be implicit for most **closed loop**



A



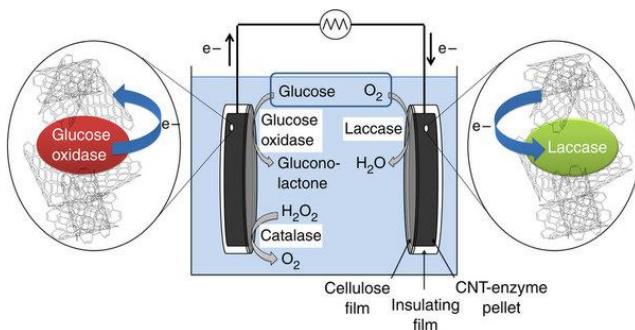
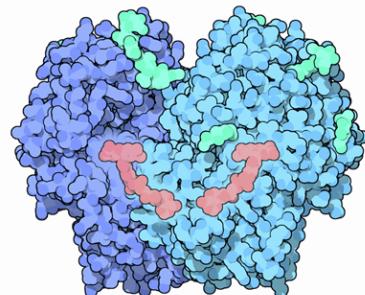
B



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

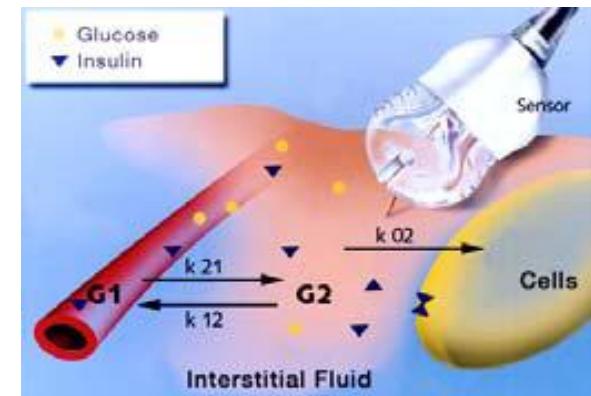
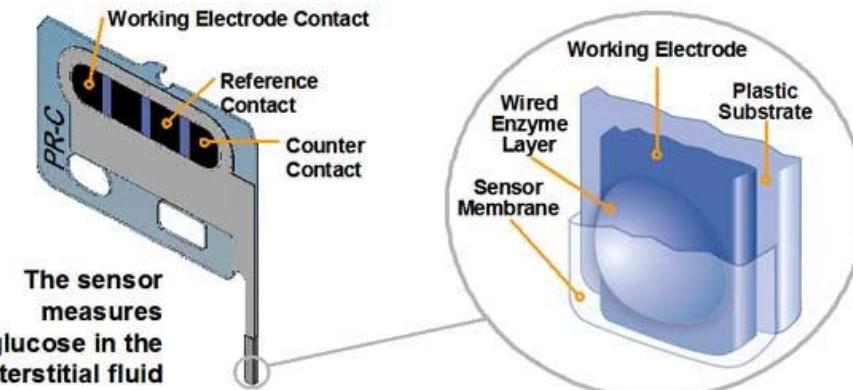


- sensor integrated with Smart phones



continuous monitoring

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





sensor progression

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



The C8 MediSensors Experience



Continuous View
You can't control what you can't see. C8 MediSensors technology is designed to deliver glucose measurements continually throughout your day. As frequently as every five minutes.



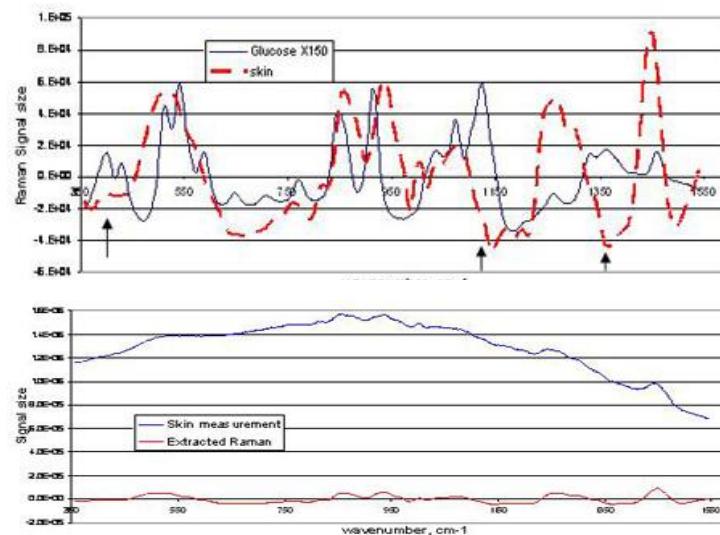
Discretion
Comfortably and modestly monitor your glucose. The adjustable band is fashioned to be worn under the clothes so the monitor can disappear from view. You can get constant glucose measurements with complete discretion.



Smartphone Display
Continuous readings are sent to your smartphone, so you can see your status at a glance. View 3 hours of readings instantly and 4 months historical readings with the swipe of a finger. Set high and low thresholds for alerts. And have one less bulky item in your pocket.



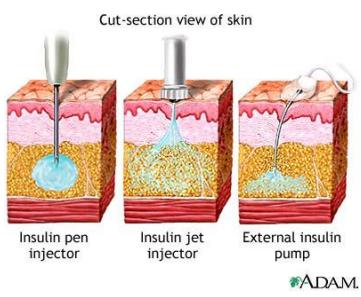
Accuracy
In clinical studies, the C8 MediSensors Optical Glucose Monitor™ demonstrated accuracy comparable to published accuracy reports for invasive continuous glucose monitors.





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 (Tandem)
- barriers to success





patch pumps

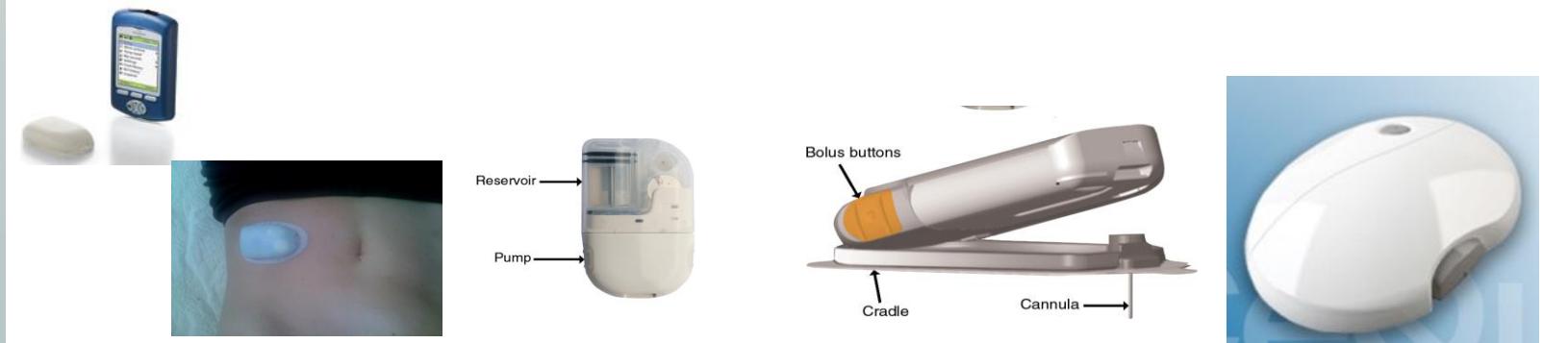
- connects with very short tube at the back
- seems more acceptable



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



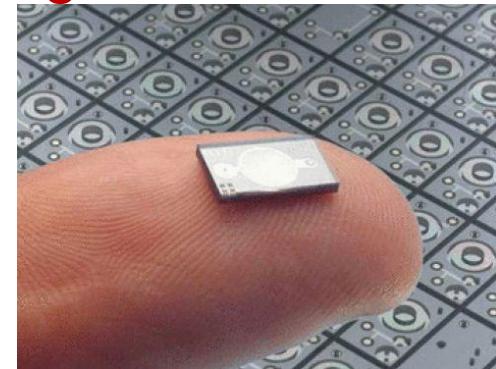


patch pumps

- Micropump Debiotech Jewel
- dimension ratio



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





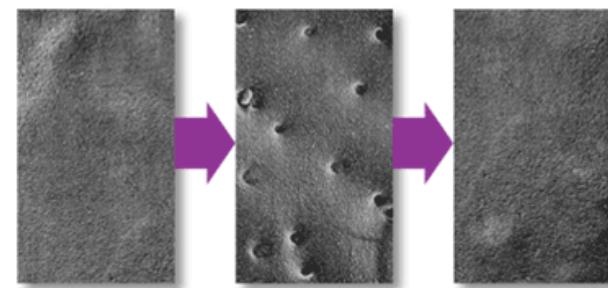
patch pumps

■ Altea –the electroporation Passport

- needle and cannula-free
- delivery local or means to systemic
- may now be defunct



The phenomenon of electroporation

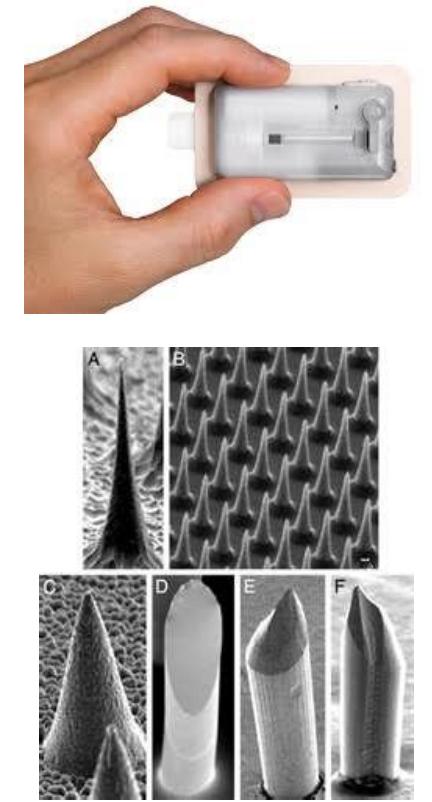
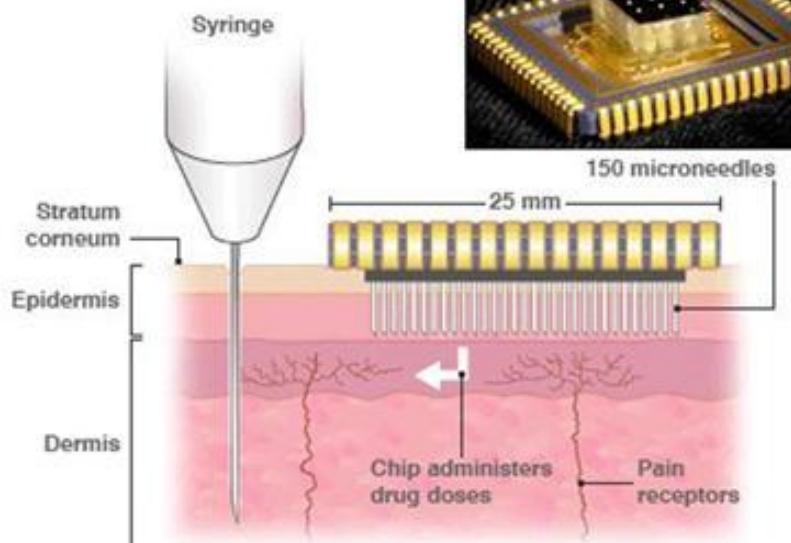


- Controlled, millisecond electrical pulses induce temporary pores in the cell membrane
- Cell membrane reseals and is left unharmed

patch pumps

- microneedle technology
- Valeritas V-Go

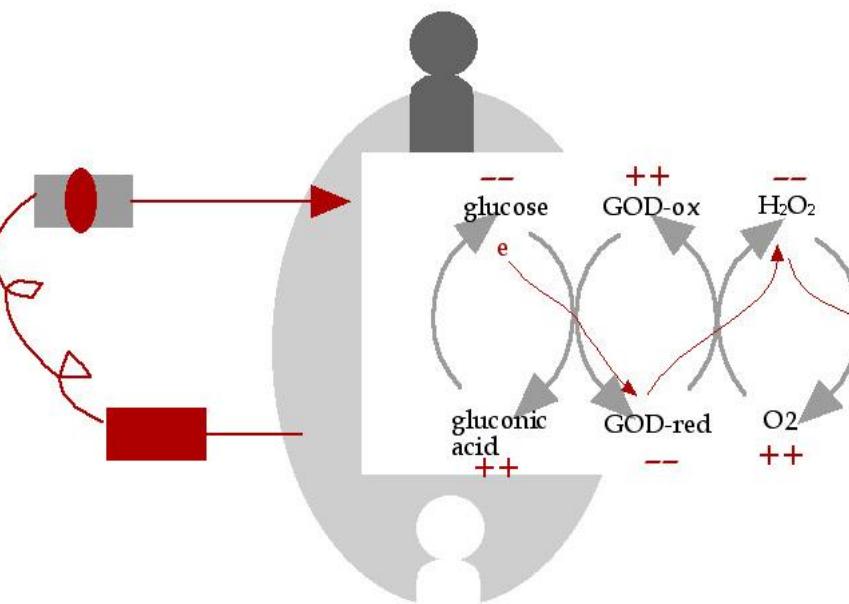
MICRONEEDLES DRUG PATCH



integrated sensor and pump

■ more about direct contact sensor problems

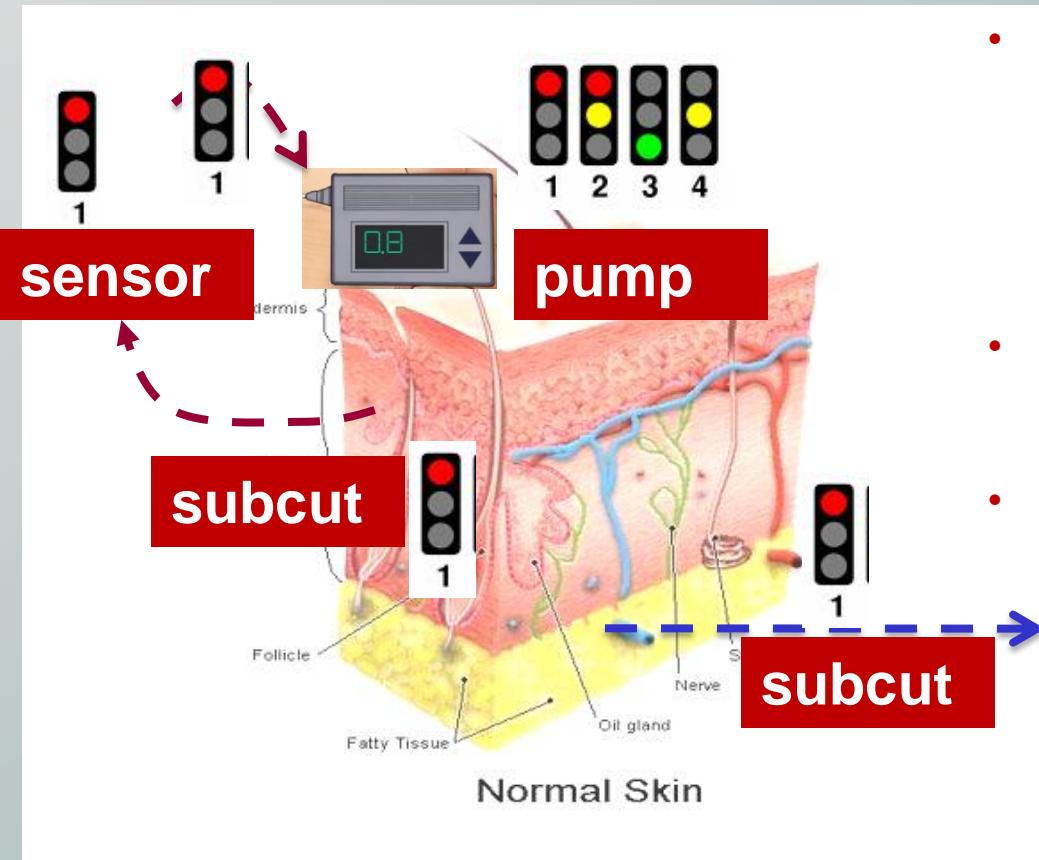
microprocessor controlled pumps
linked to electronic glucose sensors



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**

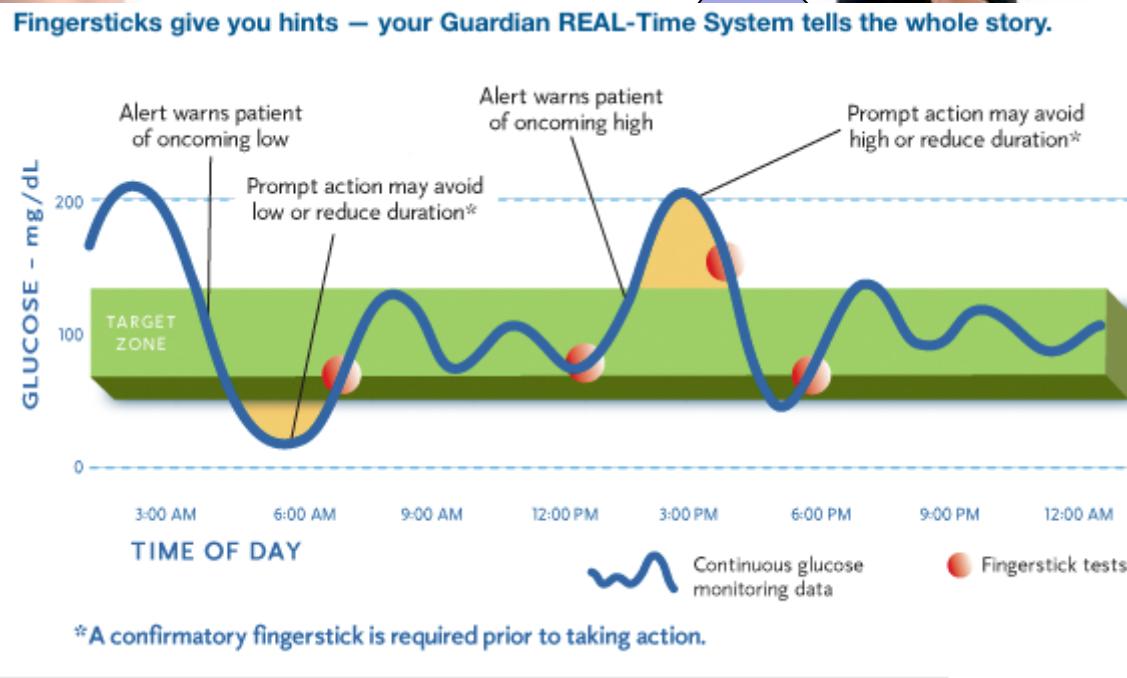
subcutaneous delay



- 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



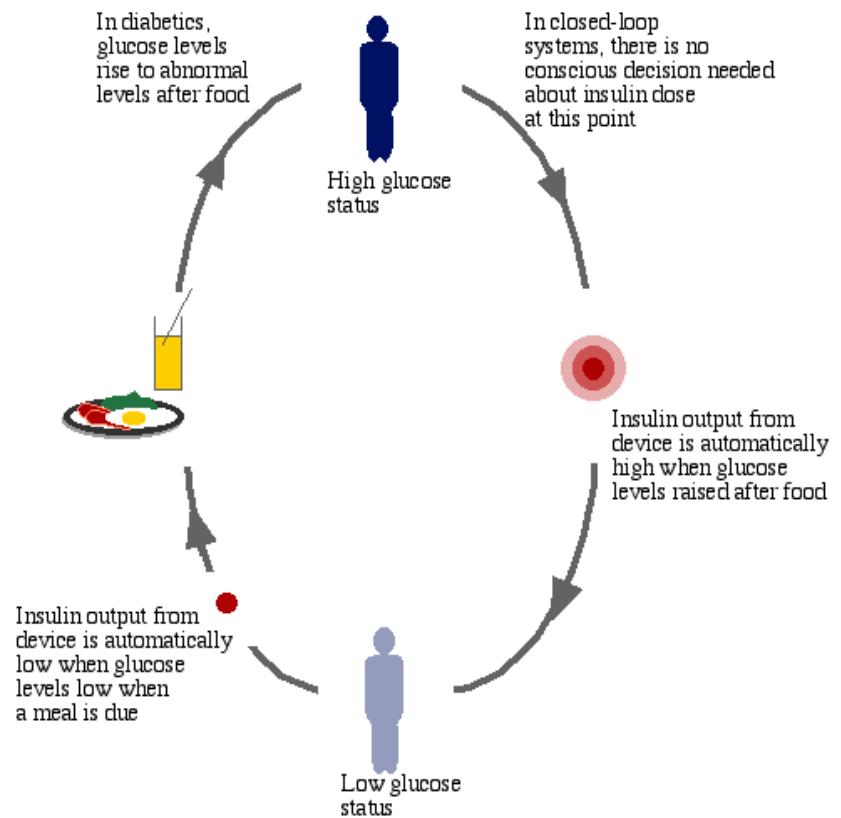
smart loop is still mainly open



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

■ glucose monitoring

■ insulin infusion

■ meal detection

■ exercise detection



B

Wizard - Add glucose measurement

Glucose measurement: 6.3 mmol/l

Date: 20/08/2008 Time: 07:00

C

Confirm or modify insulin advice

Insulin infusion: 1.3 U/h

Next measurement in: 14 min

A



1 → B → C → 3

D

Subject: S03_09_01AG, 78 kg, ID:

glucose (mmol/l) insulin infusion (U/h)

19:00 21:00 23:00 01:00 03:00 05:00 07:00

15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0

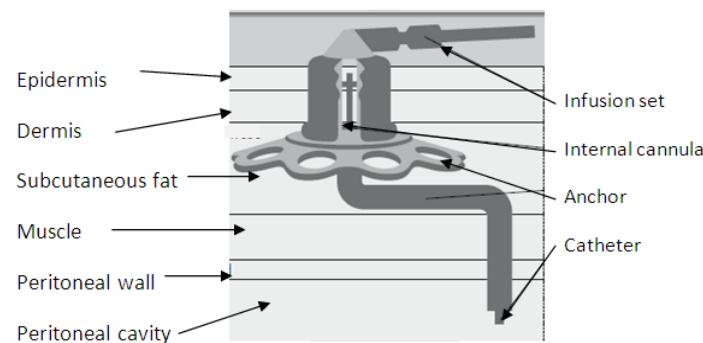
5
4
3
2
1
0

Dashed red lines indicate target glucose range (4.5-8.0 mmol/l).



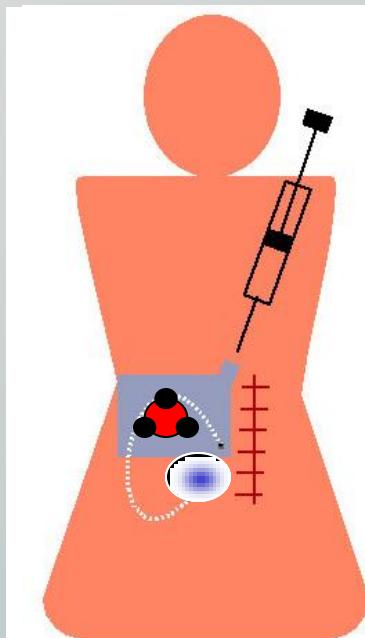
the Diaport

■ peritoneal delivery by external infusion





IN smart totally implantable pump

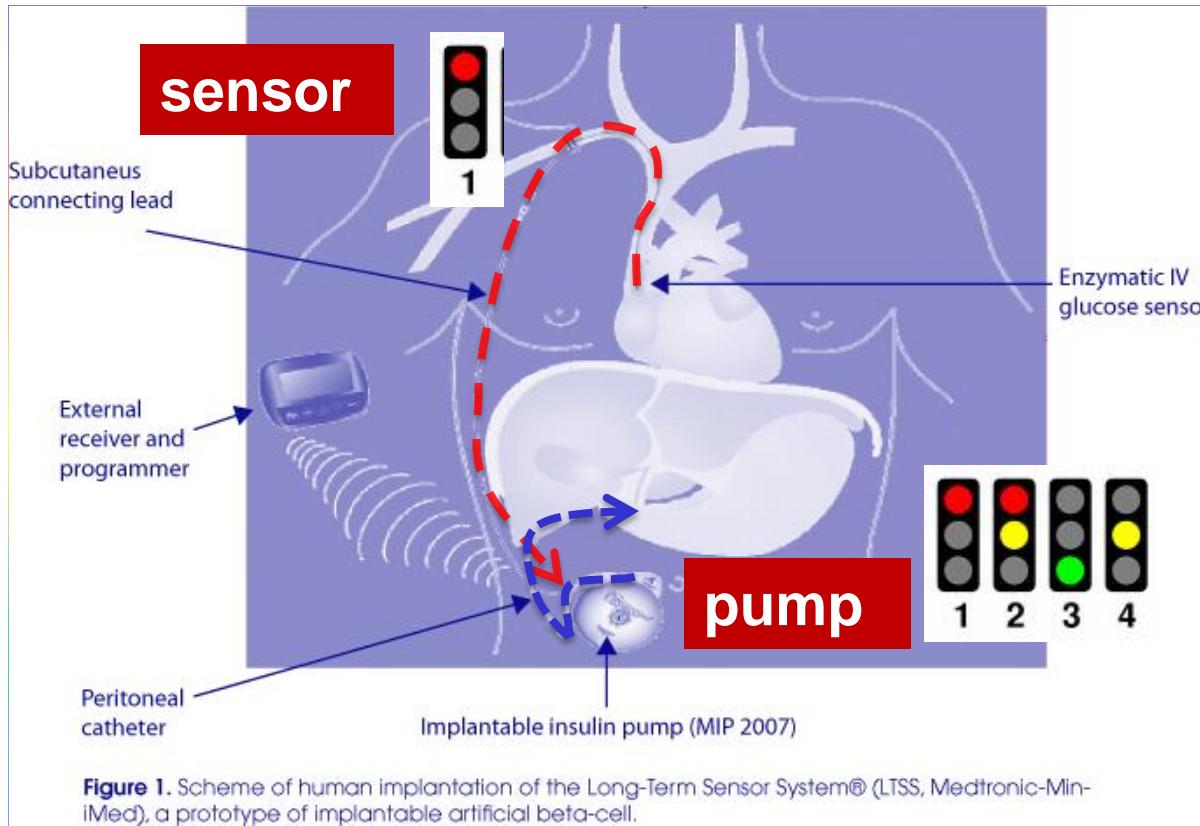


- at first was mainly programmable
- refillable
- has now been adapted to closed loop with an implanted sensor coupled to a microprocessor vascular & subcutaneous sensors trialled





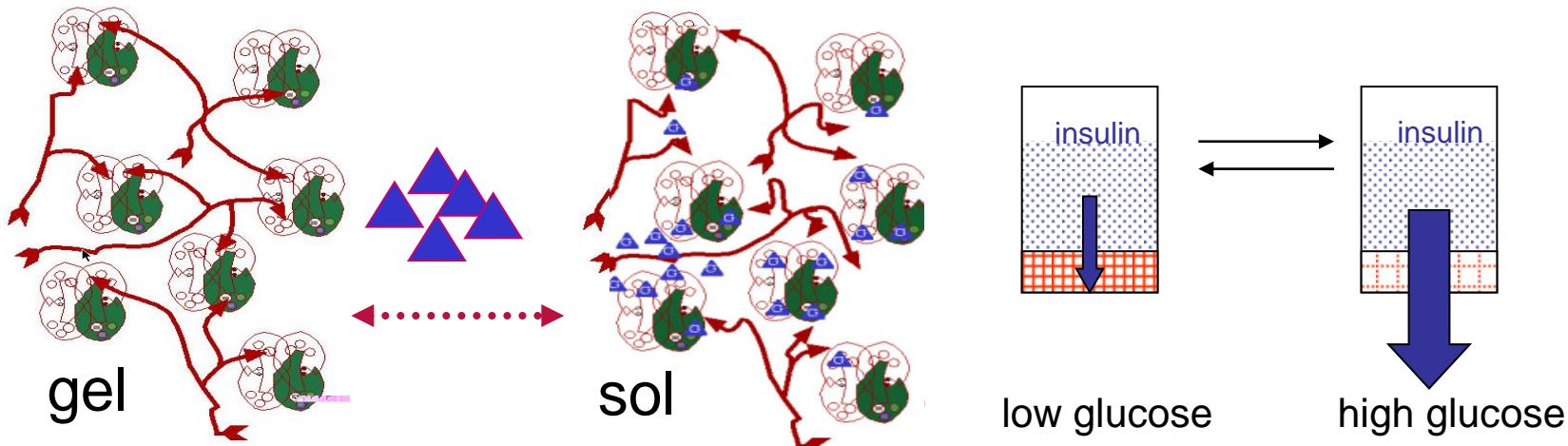
totally implantable pump



our technology

■ device with glucose sensitive gel

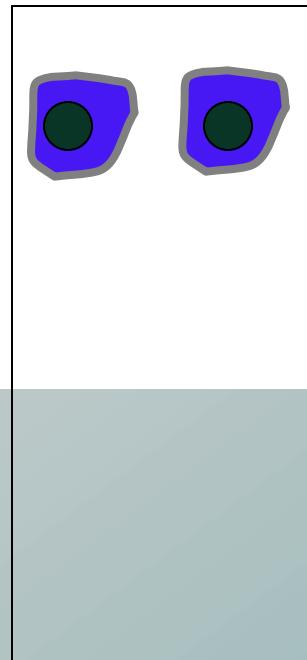
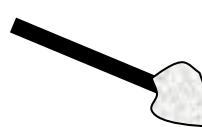
- governs output from insulin depot



- 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

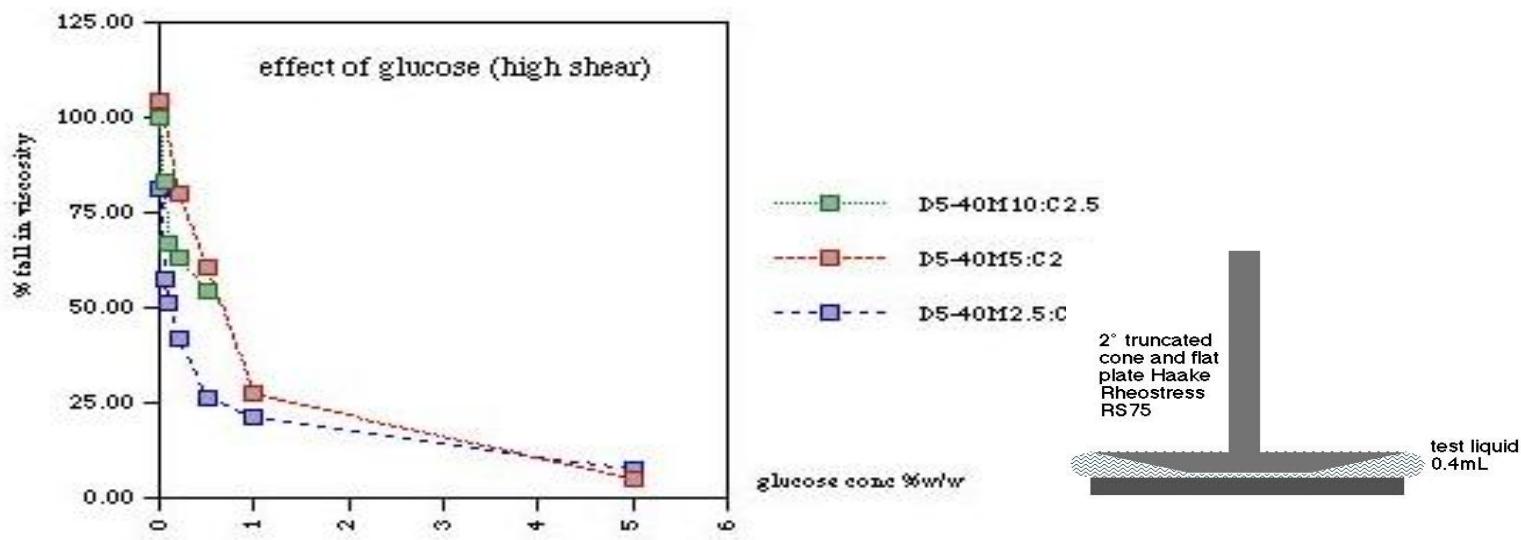
dry glucose
added



our technology

■ in vitro evidence

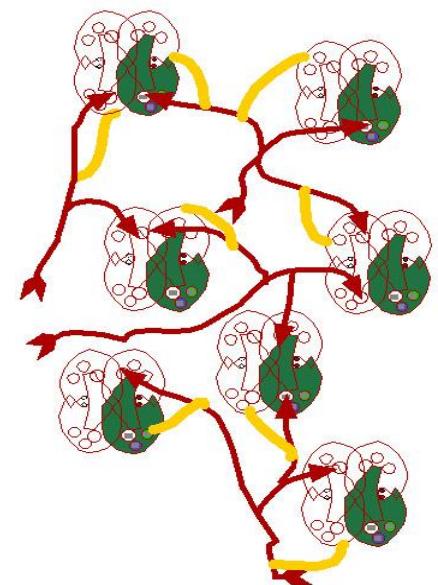
- measuring the viscosity changes
 - using standard methods
 - viscosity falls over relevant values



our technology

■ improving the basic mechanism

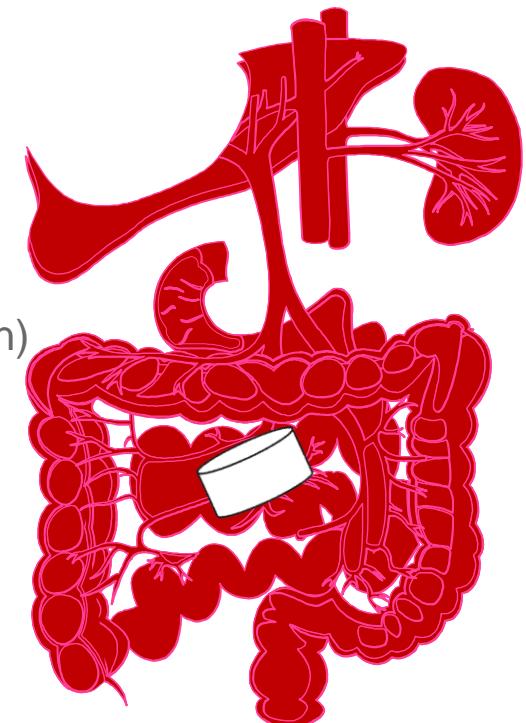
- component movement
 - loss and phase separation
 - could disable mechanism
 - could be toxic
- remedies
 - bond molecules together
 - standard covalent bonding & polymerisation
 - small pore size





the peritoneal site

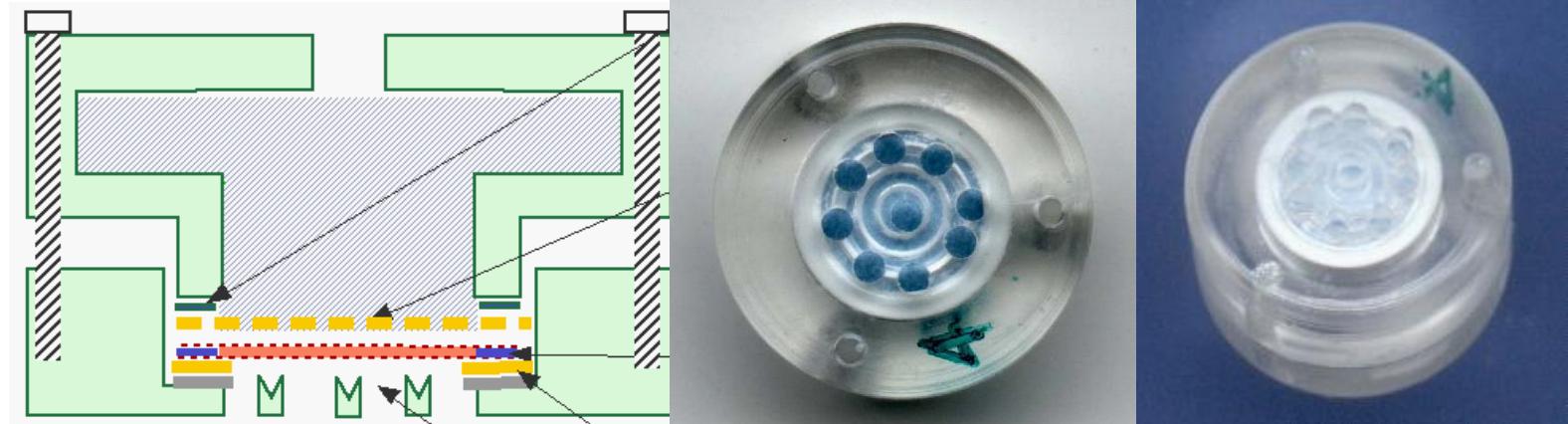
- allows **sensing** of ambient glucose
 - glucose equilibrium blood:peritoneal fluid
 - delivery is always appropriate
- allows **delivery** directly to liver
 - small aliquots
 - fast, not rate-determining
 - mesenteric veins drain peritoneum (cf skin)
 - mesenteric to portal to liver route
- metabolism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



rat trials device

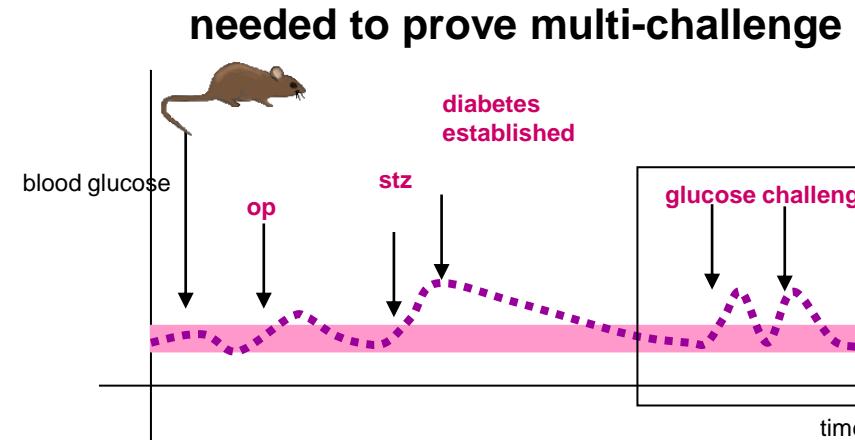
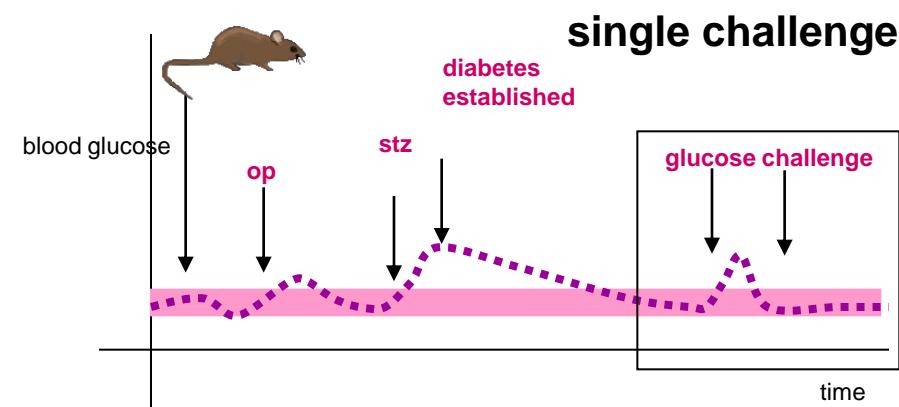
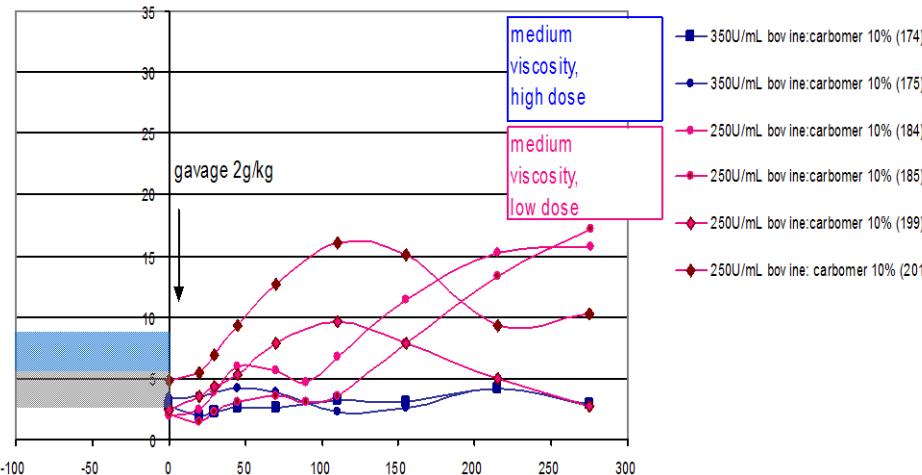
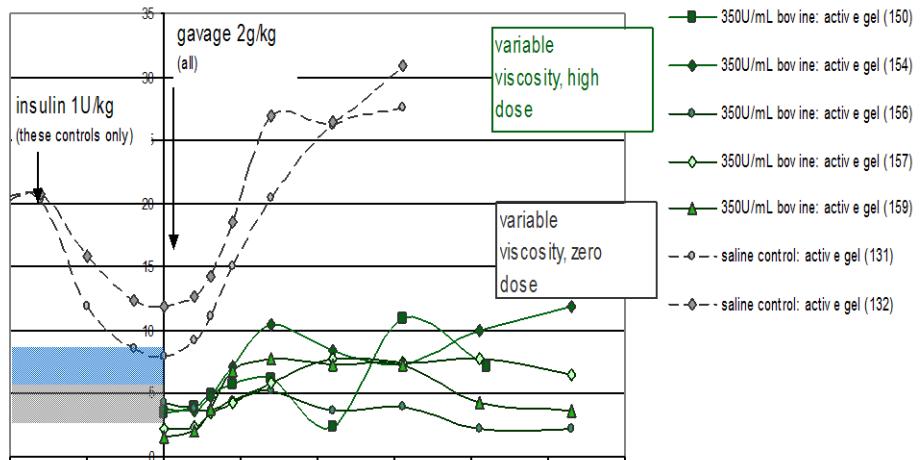
■ testing the feedback

- building simple in vivo test cell
- for peritoneal implant



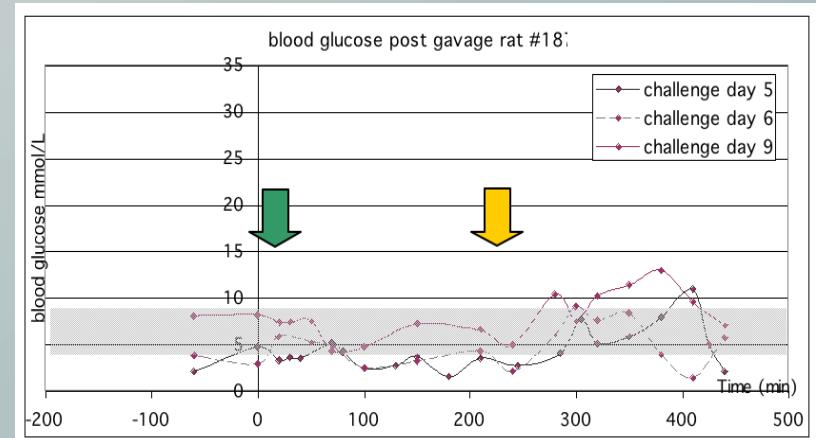
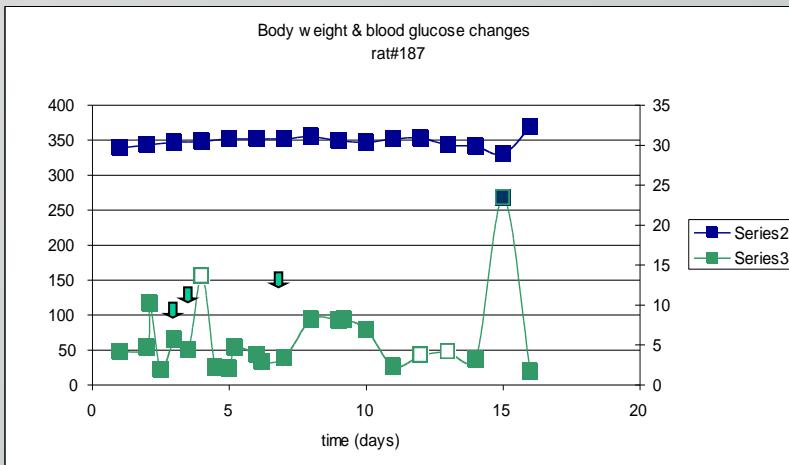
rat trials

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



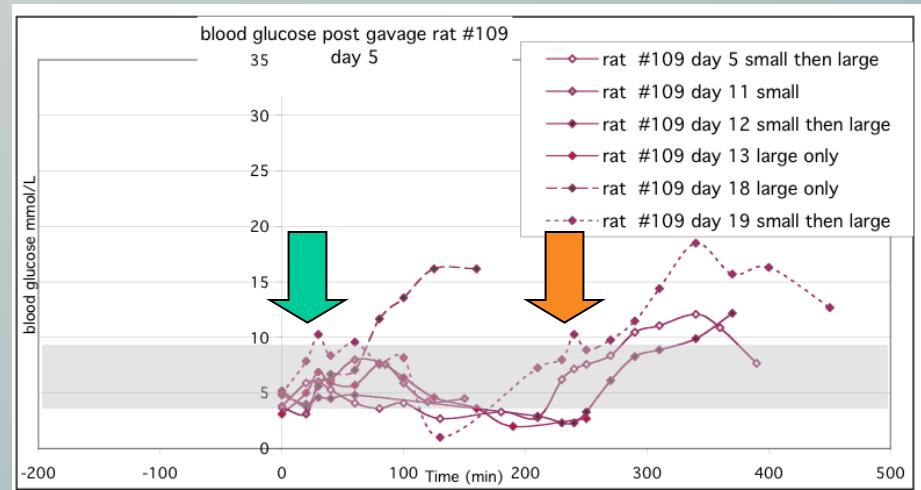
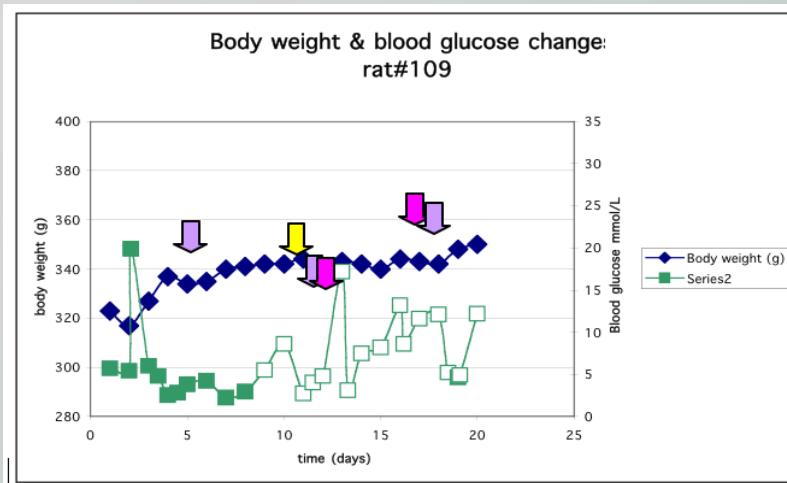


multi-challenge tests



- 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

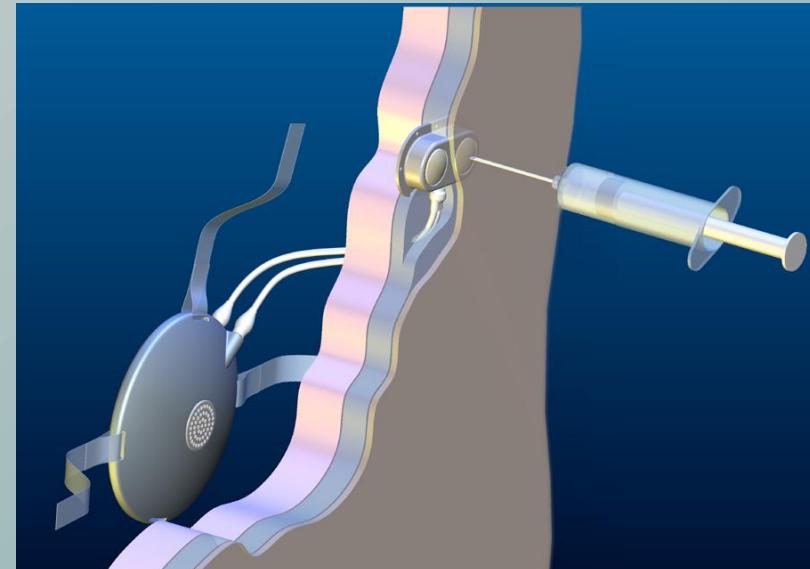


- successfully exposing failure of control experiments
 - also affected by calorie intake and output
 - but withholding food suppresses peaks
 - repeated challenges reveal lack of control
 - as seen here in this long lasting control experiment



clinical design

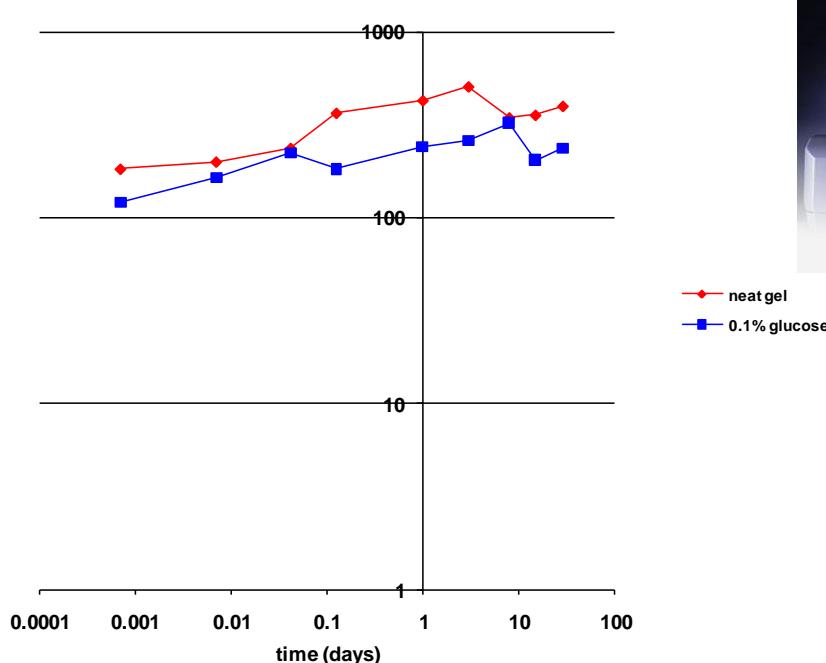
- simple 'closed loop' pump
 - based on a chemical response
 - glucose-specific one-step response
 - responds rapidly and in therapeutic range
 - no biological, electronic or moving parts
 - needs no battery power
 - needs no immunosuppressive drugs
 - could be available in large numbers
 - could be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



gel stability

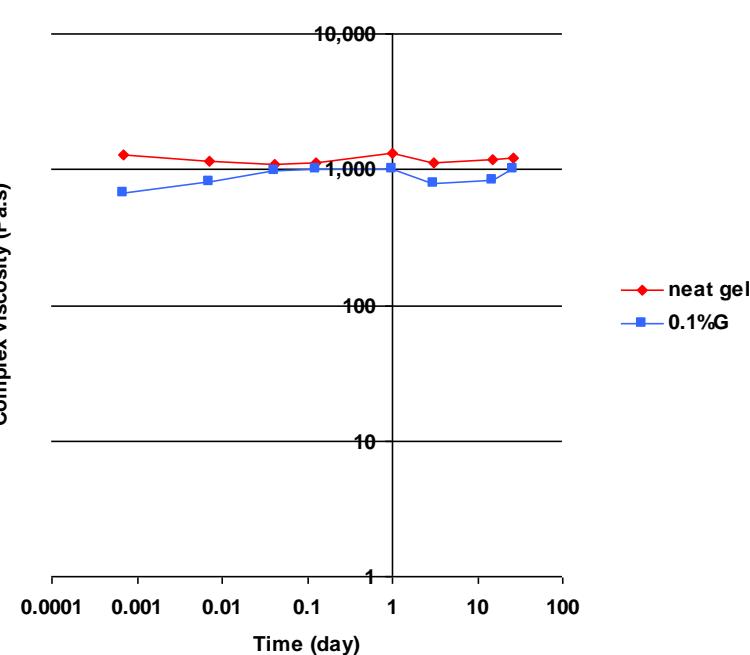
D500 + con A raw gel over time

Complex viscosity (Pa.s)



D500-MA+con A-MA acrylic gel irradiated for 50 min

Complex viscosity (Pa.s)

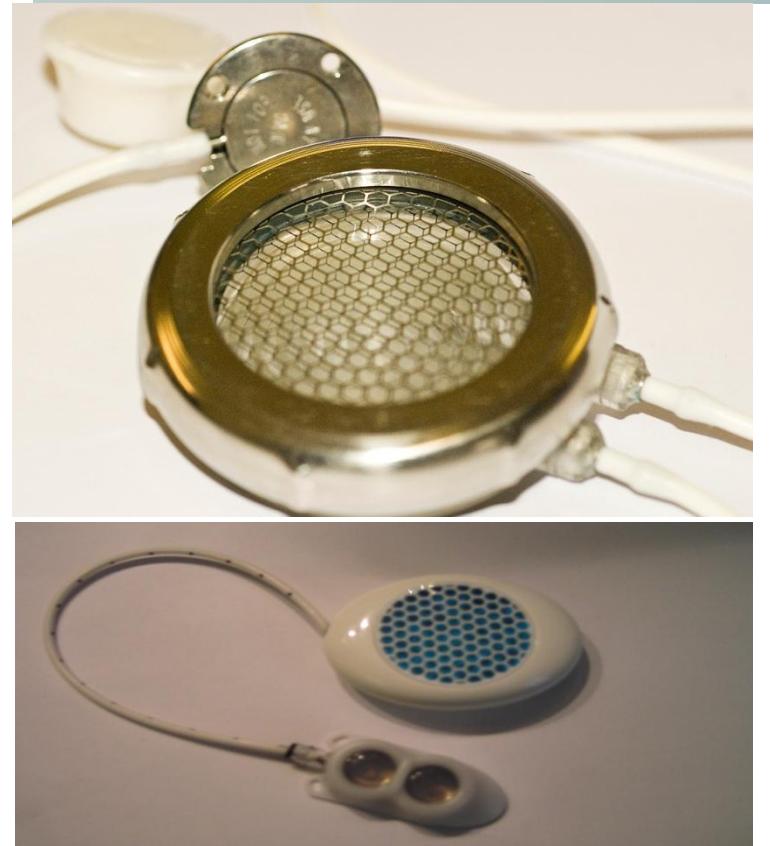


- method –dialysis bags
- creatinine (132mmol/L), lactic dehydrogenase147U/ml), albumin(21.2g/L), bilirubin (305mmol/L), triglycerides (0.7mmol/L), cholesterol (1.7mmol/L), glutamic oxalatic transaminase(40U/L)
- chymotrypsin could breakdown con A into peptides and amino acids

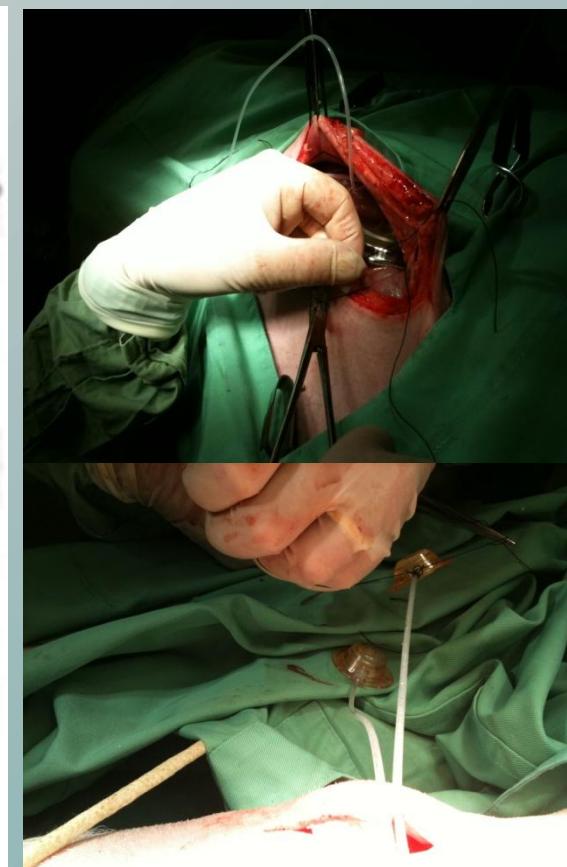
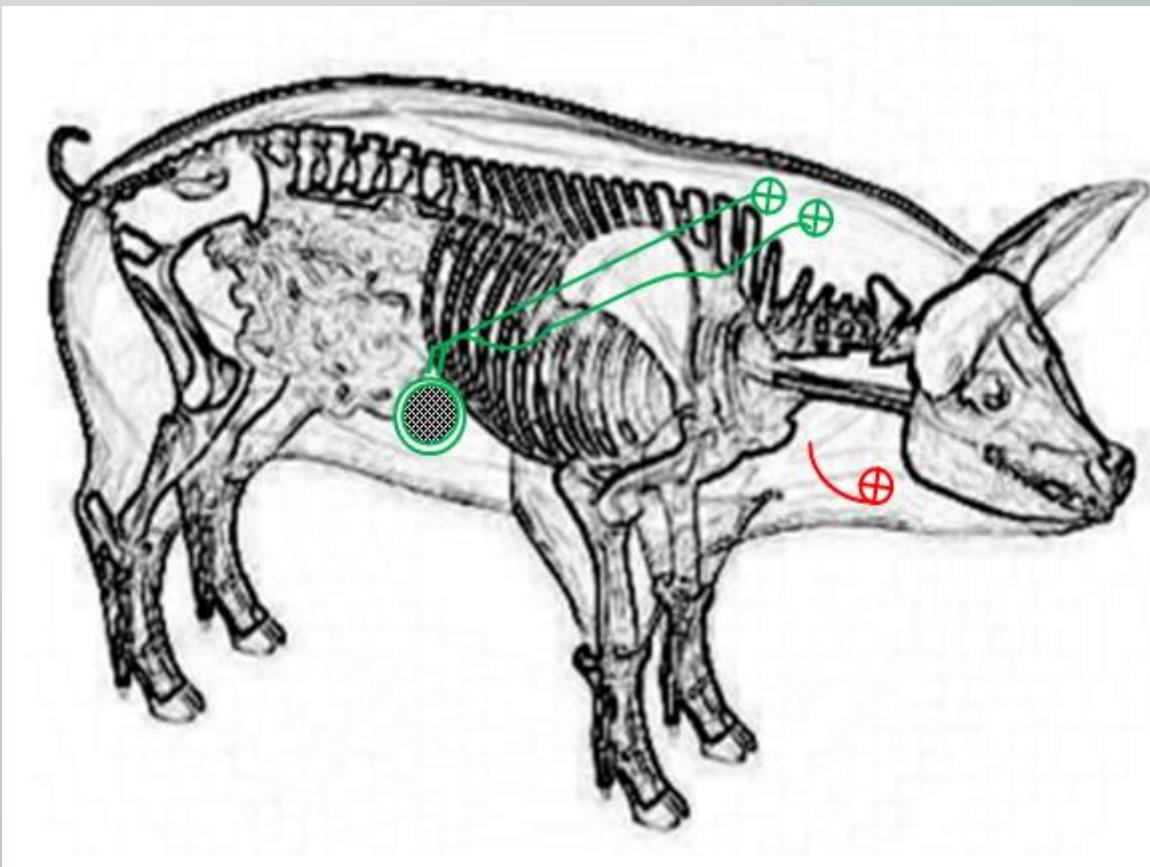


pig device & clinical maquette

- 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



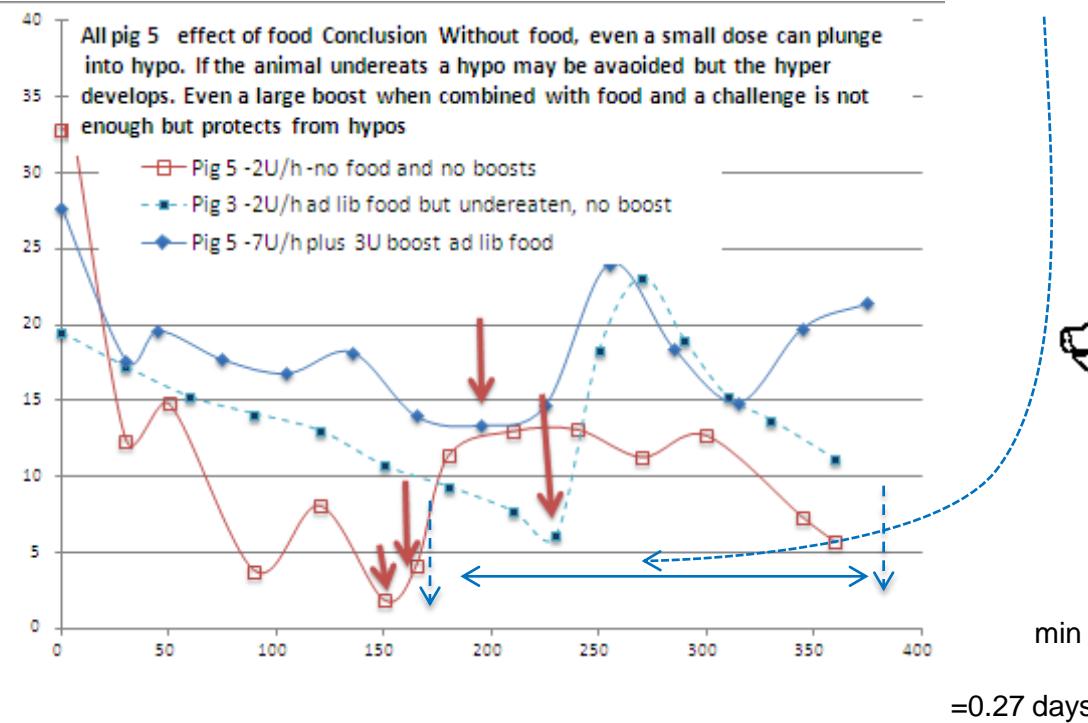
pig trials



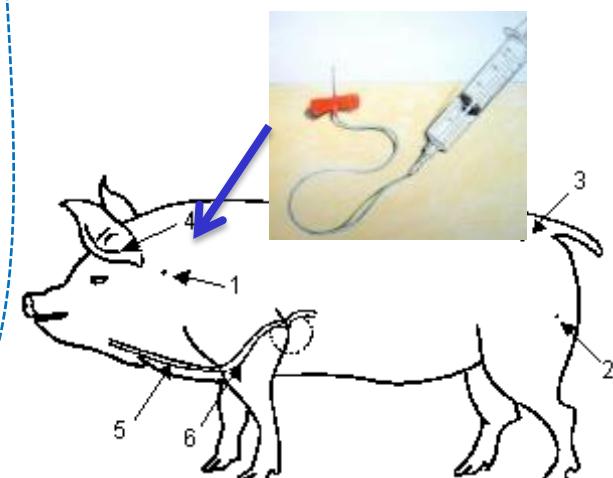


pig trials

iv calibration



hours well above normal

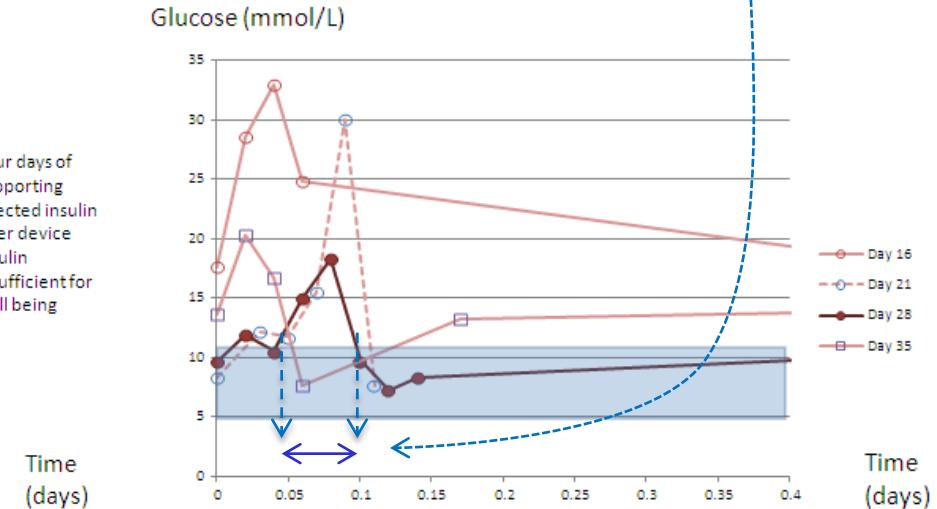
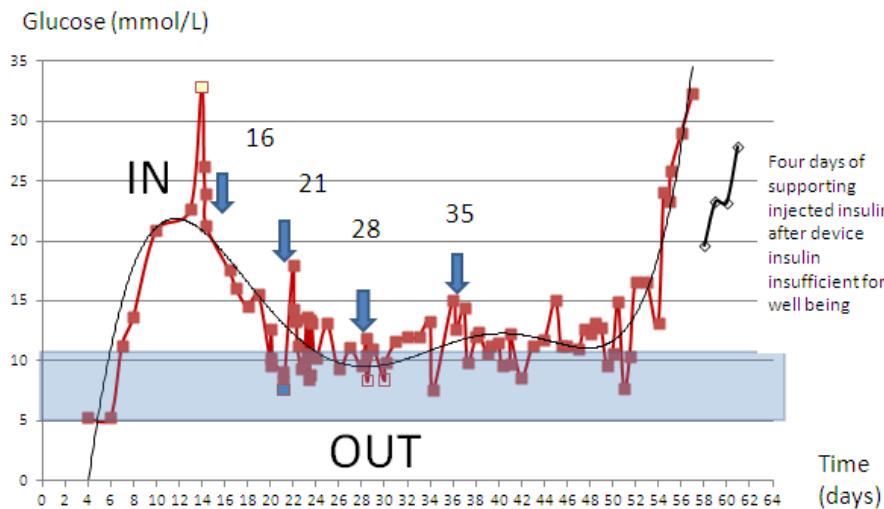


pig trials

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

