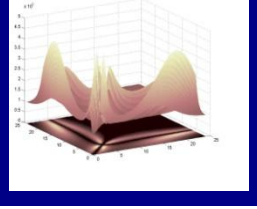


Designing a pilot study using adaptive DP-optimality

Abhishek Gulati

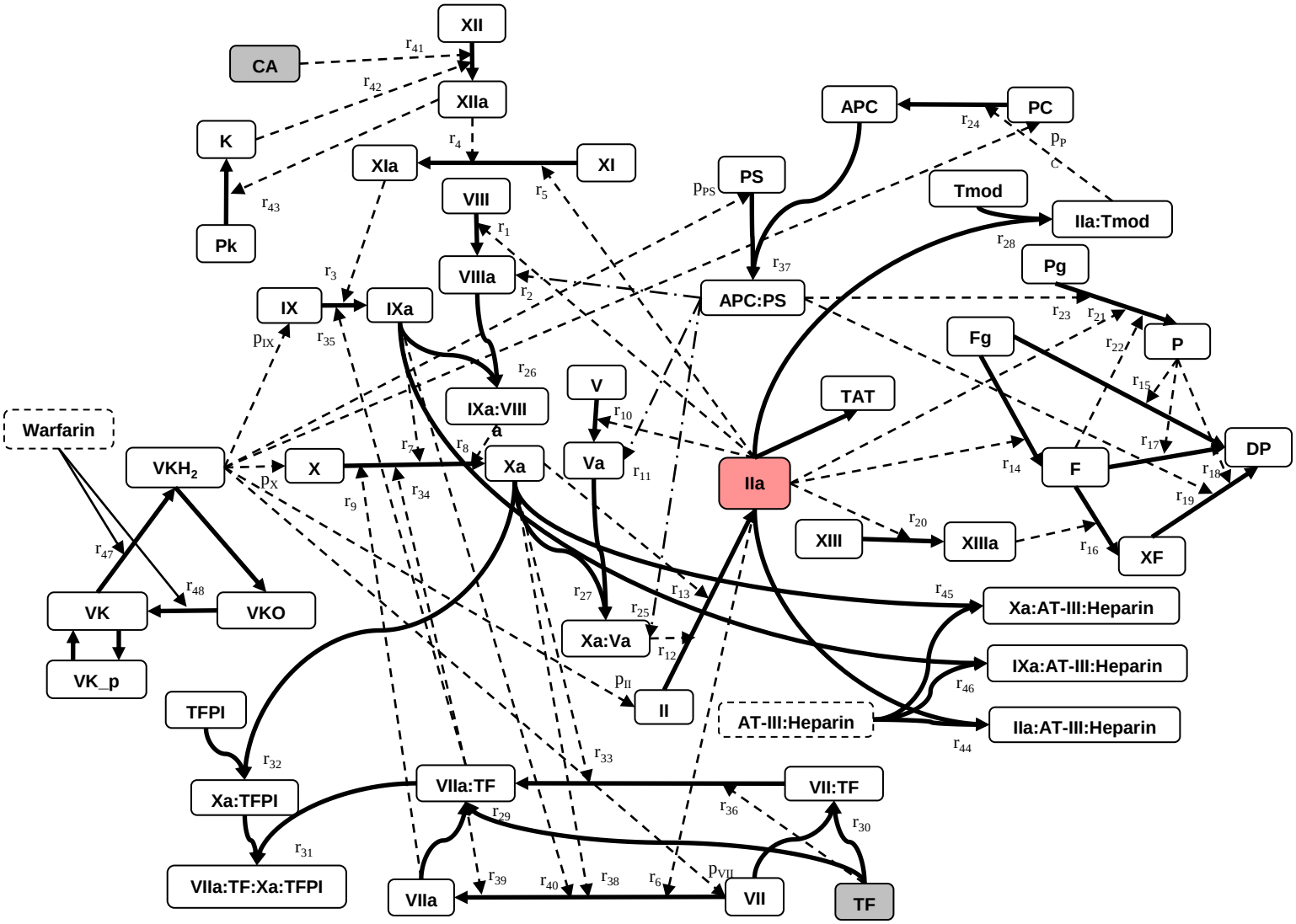
Stephen Duffull

PODE, 2013

Context - health

- Low molecular weight heparin drugs (e.g. enoxaparin) are used acutely in the treatment of various cardiovascular diseases
  - For example, heart attacks, deep vein thrombosis
- They act by reducing blood clot formation which encourages clots to resolve
- Too much → bleeding
- Too little → further clots
- A test is needed to assess bleeding/clotting risk so we can get the dose correct

Clotting is complex and complicated



A clotting time test

- The test is based on the notion that if you reduce the ability of the blood to form a clot then the time to clot (clotting time) will be prolonged.
- The degree of prolongation will determine the therapeutic or toxic potential of the anticoagulant (enoxaparin).
  - A clotting time of 10-20 seconds is normal.
  - A clotting time of 40 to 80 seconds is therapeutic
  - A clotting time of > 80 seconds may result in bleeding
- Note for a patient with a clotting disorder a normal clotting time may result in further clot formation.

Development of a clotting test

Proof-of-mechanism study
(*in-silico* and an *in-vitro n-of-1* experiment)

↓

Pilot study
(6 healthy volunteers)

↓

Proof-of-concept study
(20 healthy volunteers)

↓

Evaluation in patients

...

Why the pilot?

- The proof-of-mechanism supported the thesis that we postulated for setting up a test,
- However the curse of heterogeneity resulted in the test not performing well in subsequent individuals
  - Significant variability in clotting time responses between individuals
- A pilot study was needed to determine the experimental conditions under which its performance would be acceptable across a wider range of individuals
- Two factors {Xa, Z} were considered as design variables.

The factors

- Xa is used to cause an *in-vitro* clot.
  - Too little and the clot doesn't occur
  - Too much and the clot occurs too fast and is insensitive to enoxaparin

- Z is used to reduce variability of the clotting time response for the *in-vitro* clot.
  - Too little and it doesn't work
  - Too much and Z causes a clot to occur of its own accord.

The pilot experiment

- A blood sample is taken from a subject
- The sample is split into different vials and 4 known amounts of enoxaparin are added to provide concentrations of {0, 0.25, 0.5, 1.0} U/mL
- The two factors of interest are added (Xa & Z)
- The time for the blood to form a clot is measured (= clotting time)
- Only a single combination of Xa and Z to be used per subject
- *We can only study 6 subjects for the pilot*

Methods for choosing values of Xa & Z

- Minimax design
  - Choose values that minimize the maximal variance in the experimental cases
- Factorial design
  - Consider a design that factors across all reasonable values
- Adaptive design
  - Consider a method to determine the probability of success over any values of Xa, Z by modelling the response surface

The response surface

- The response surface is described by a parametric function with unknown parameter vector (β)
- A surface will be determined for each of the 4 concentrations of the anticoagulant enoxaparin {0, 0.25, 0.5, 1}
- From these 4 surfaces a utility function can be applied that determines the overall success or failure of the test

The adaptive design

- The parameters are estimated using an adaptive design
- This method is linked to D-optimality for parameter estimation.
- It is also important for the pilot study to provide some empirical evidence of the utility of the test and for this purpose we used P-optimality (to optimise the probability of experimental success)
- A utility function was used to incorporate experimental success

Aim

- To conduct a pilot study with 6 subjects to determine values of {Xa, Z} to take forward into a proof-of-concept study

Response surface

$$CT = \left(\frac{f_Z^{\,2}}{f_E^{\,5}} a \right) f_{Xa}^{\,b}$$

$$f_{Xa} = 1 - \frac{[Xa]}{\left(\frac{f_E}{f_Z} K_{DXa} \right) + [Xa]}$$

$$f_E = 1 - \frac{[enoxaparin]}{K_{DE} + [enoxaparin]}$$

$$f_Z = 1 - \frac{[Z]}{K_{DZ} + [Z]}$$

The response surface (CT) over values of Xa and Z is determined for each concentration value of enoxaparin {0, 0.25, 0.5, 1}

Parameters, $\boldsymbol{\beta} = \{a, b, K_{DE}, K_{DZ}\}$

Formulating a utility from a set of response surfaces

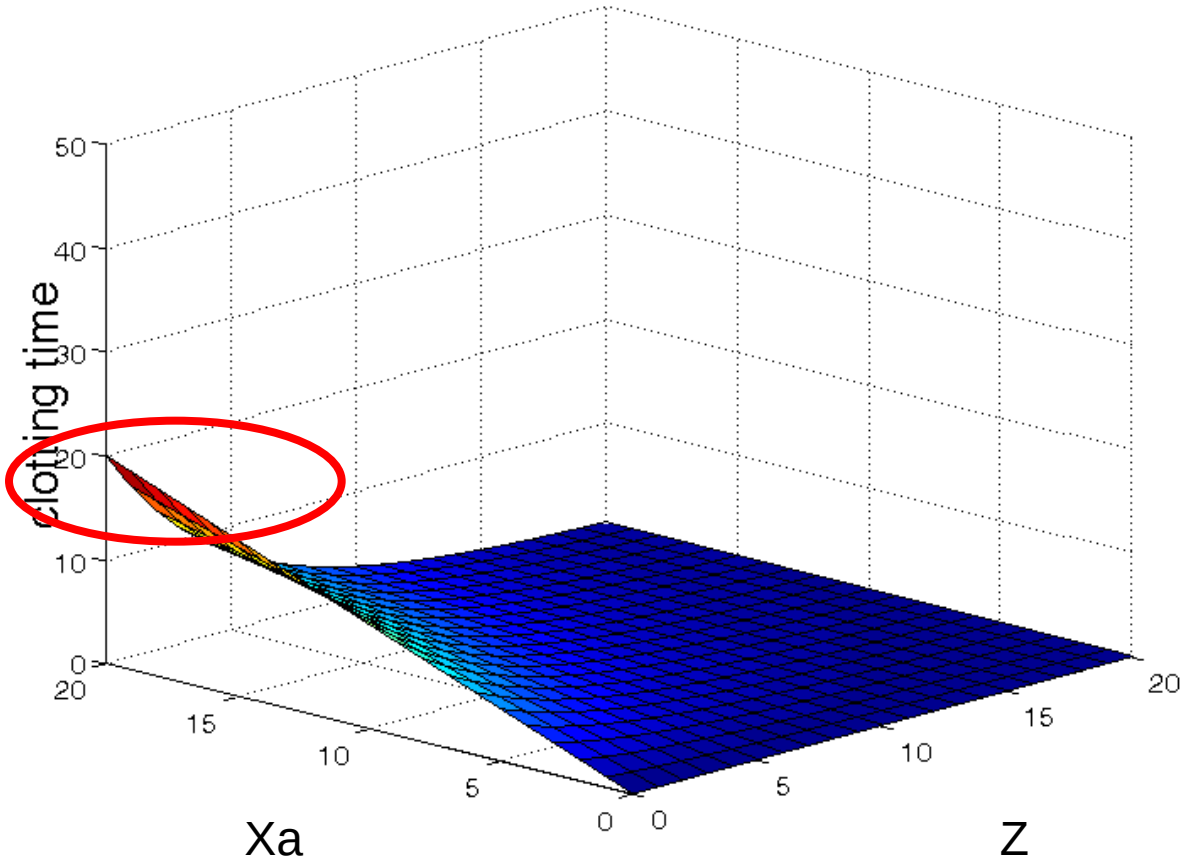
- The response surface will be determined for each of the 4 concentrations of enoxaparin.
- The response surface is characterised by a particular clotting time over a range of values of Xa and Z.
- Values of the clotting time that are desirable are then determined so that a utility can be formed.
  - High utility = appropriate clotting times

Defining success

1. $(10s > CT > 30s) \mid (\lceil enoxaparin \rceil = 0)$
2. $(CT \text{ fold prolongation is} > 1.3) \mid (\lceil enoxaparin \rceil = 0.25)$
3. $(CT \text{ fold prolongation} > 2 \text{ fold more than CT } (\lceil enoxaparin \rceil = 0.25)) \mid (\lceil enoxaparin \rceil = 1)$
4. $(CT \text{ fold prolongation is} < 5) \mid (\lceil enoxaparin \rceil = 1)$
5. All CT values must be $< 200s$

Success = 1 when 1-5 are true

Visual assessment of conditions



DP-optimality

Design variables, $\boldsymbol{\xi} = \{\text{Xa, Z}\}$

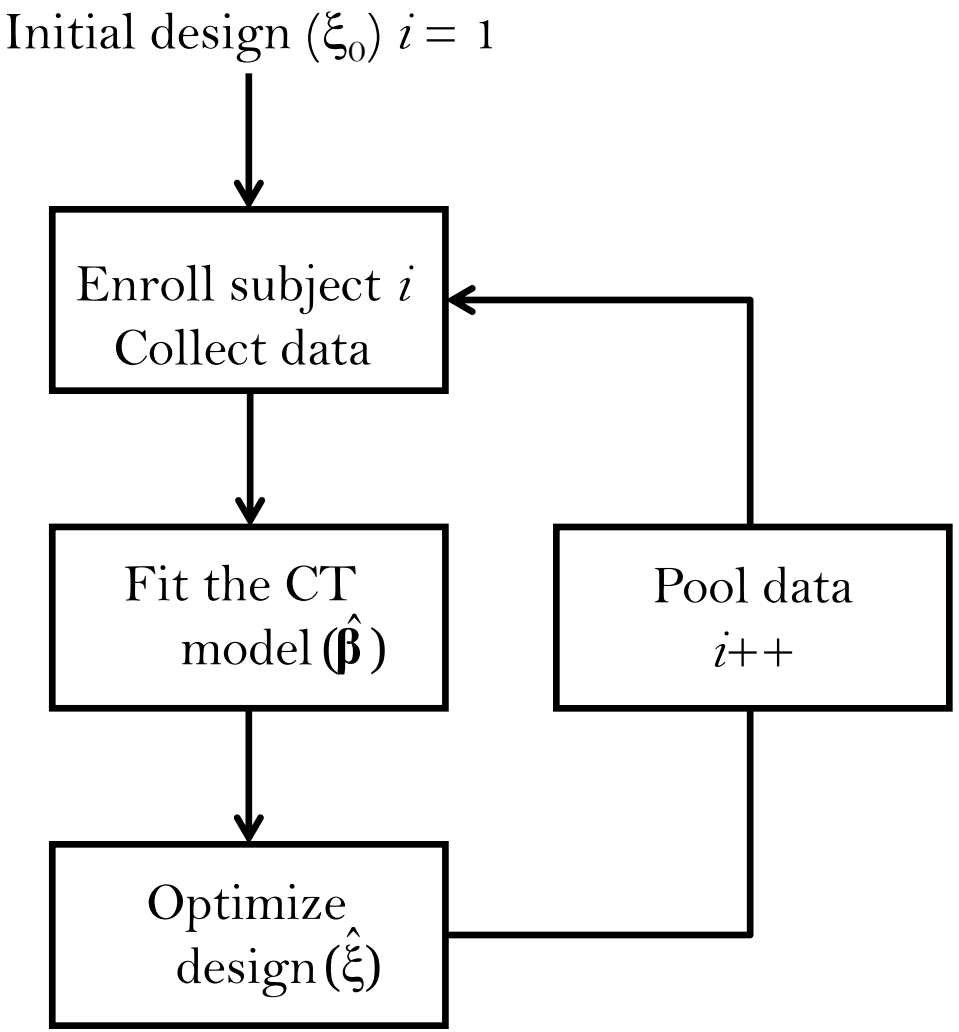
Parameters, $\boldsymbol{\beta} = \{\text{a, b, } K_{DE}, K_{DZ}\}$

$$\hat{\boldsymbol{\xi}} = \arg\max_{\boldsymbol{\xi} \in \Xi} \left(\left| M_F(\hat{\boldsymbol{\beta}}, \boldsymbol{\xi}, [enoxaparin]) \right|^{1/p} U \right)$$

$p = \text{number of parameters}$

$$U = \begin{cases} 0.9, \text{when CT success} = \text{y} \\ 0.1, \text{when CT success} = \text{n} \end{cases}$$

Adaptive design



A simulation study

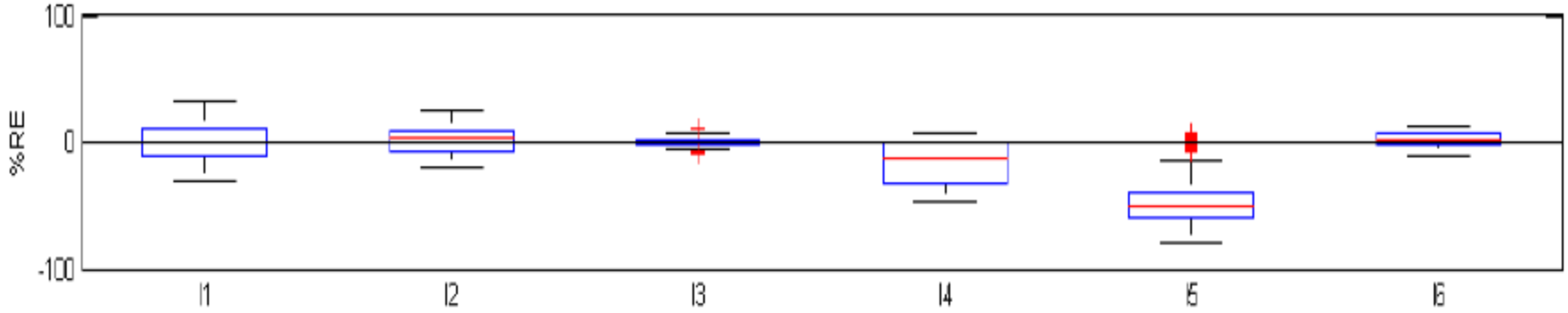
Methods

- The performance of the design were assessed by simulation
- 100 virtual trials (of 6 patients) were simulated and analysed as per the pilot study protocol
- Assessment of the precision and accuracy of parameter values were considered for both D and DP optimal designs

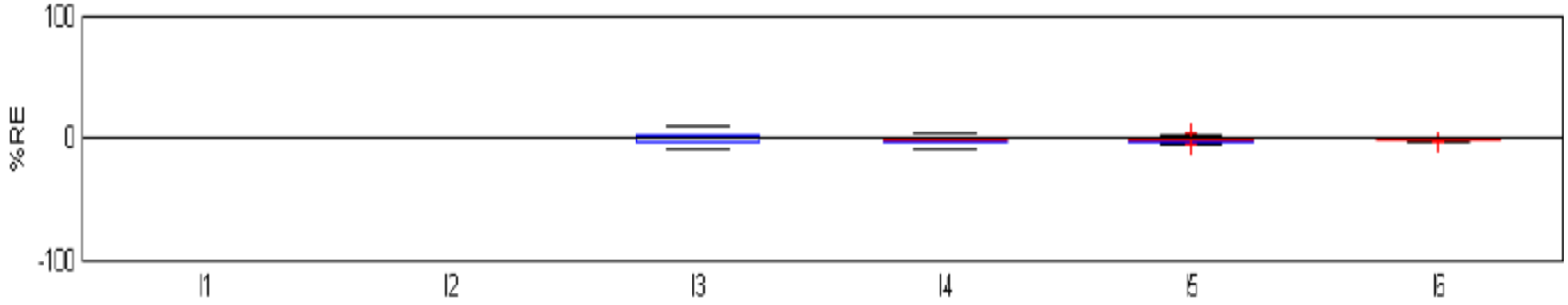
Results

- Design performance for success
  - D-optimal designs → success=y on 24% of simulations
  - DP-optimal design → success=y on 94% of simulations
- Parameter values were estimated accurately by the 5th subject
- Not all parameter values could be estimated for the first few subjects

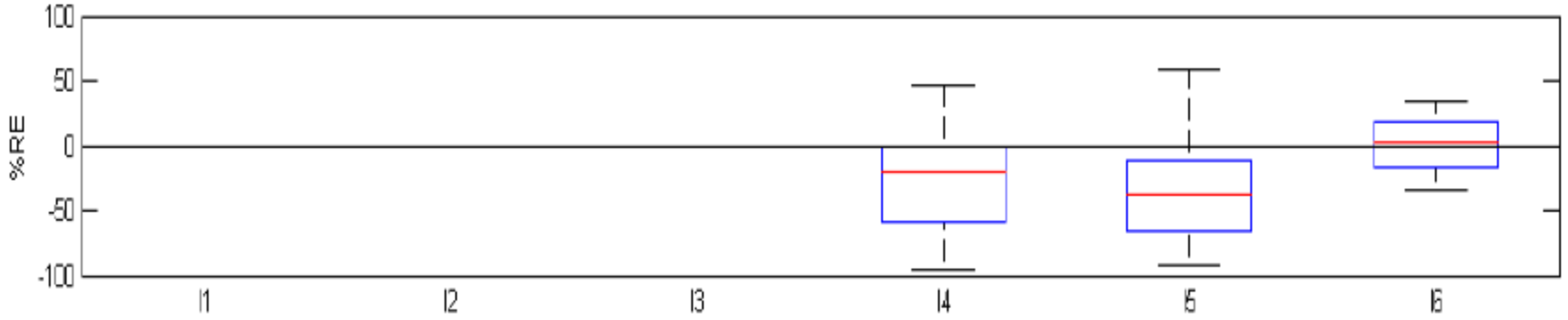
a



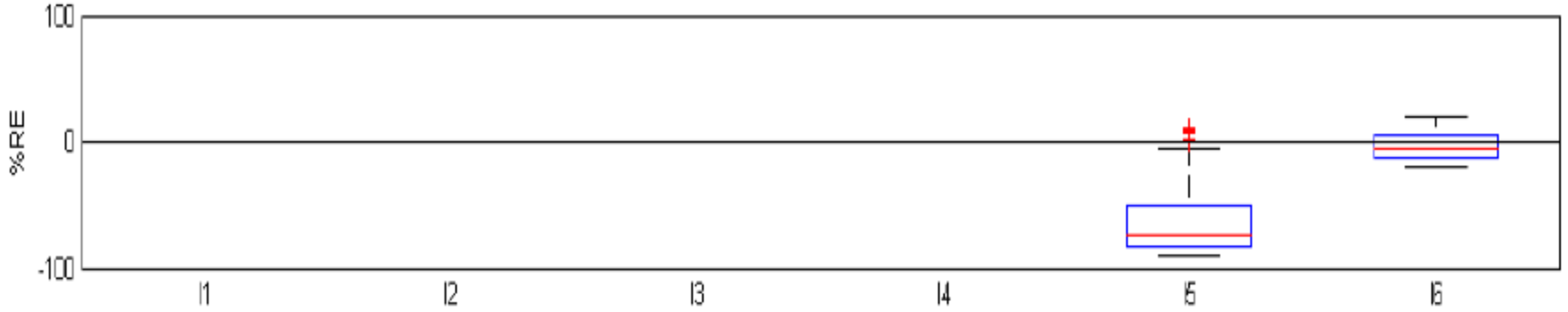
K_{DE}



b



K_{DZ}

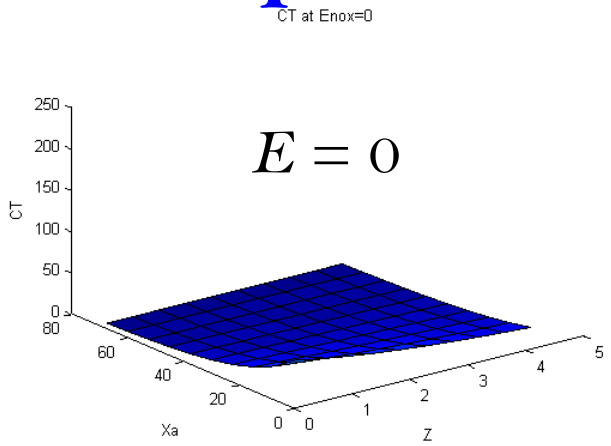


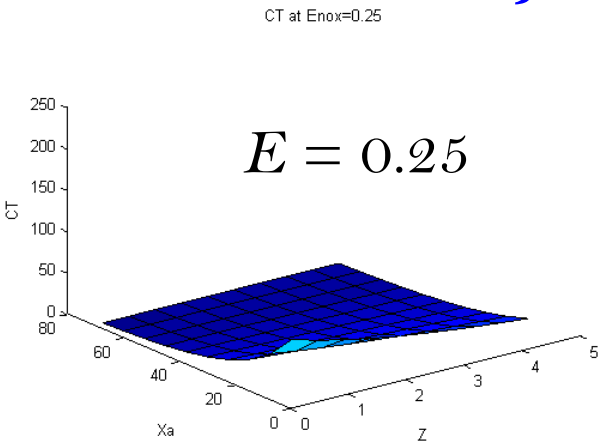
The Actual Study

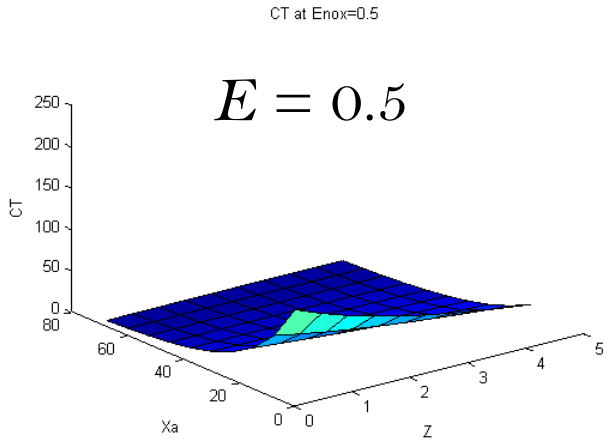
Pilot study results
Adaptive Design

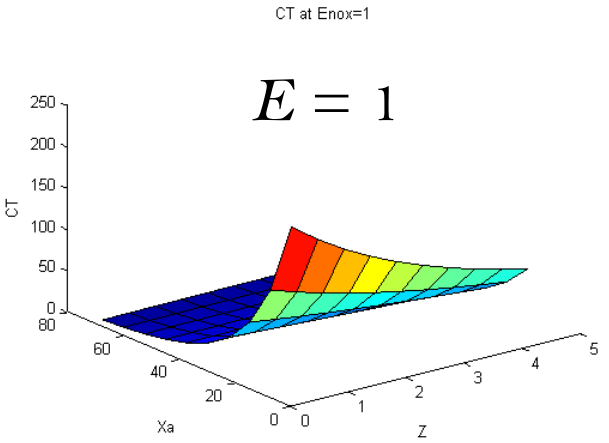
Iteration	Subjects	Design points		Parameter values			
	(pooled data)	Xa	Z	a	K_{DE}	b	K_{DZ}
1	1	15	0.80	31	-	-	-
2	1,2	15	0.80	31	-	-	-
3	1,2,3	15	0.80	42	4.2	-	-
4	1,2,3,4	15	0.80	74	3.2	10	-
5	1,2,3,4,5	15	3.3	52	3.1	11	25
6	1,2,3,4,5,6	15	0.90	60	3.1	11	7.1

Clotting time response surfaces
Enoxaparin = {0, 0.25, 0.5, 1}

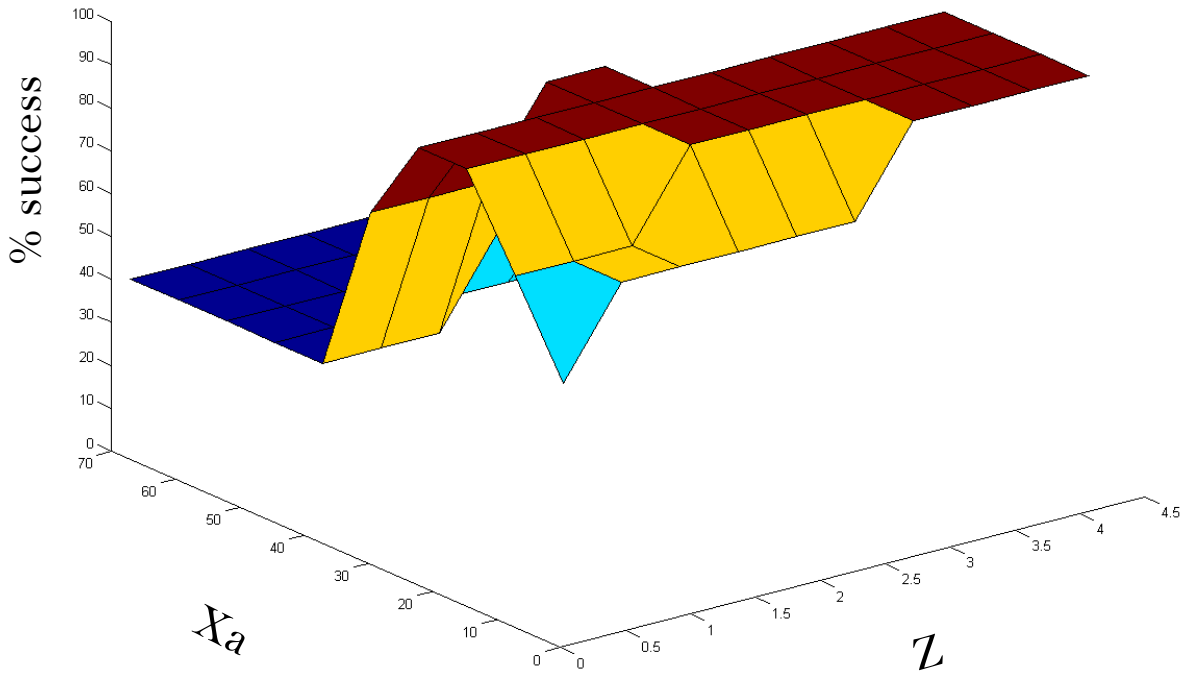








Predicted Probability of Success



Discussion

- An adaptive design using DP-optimality provided a useful method for designing the pilot study
- Fewer subjects were required than for a factorial design
- We have assumed that the parametric function provides a good description of the response surface – this was based on our understanding of the clotting system
- We have ranges of {Xa, Z} that are likely to provide a successful proof-of-concept study (just completed)

Acknowledgements

Assoc Prof Geoff Isbister

Dr Jim Faed

University of Otago Research Grant

University of Otago Postgraduate Scholarship (Abhishek)

Staff at Southern Community Laboratories, Dunedin Hospital