UC BIOMEDICAL ENGINEERING

Virtual Trials with *b-Spline* Basis Functions and Stochastic Differential Equations

Liam Fisk, Paul Docherty, Christopher Pretty, Jennifer Dickson, Geoffrey Shaw, and J. Geoffrey Chase

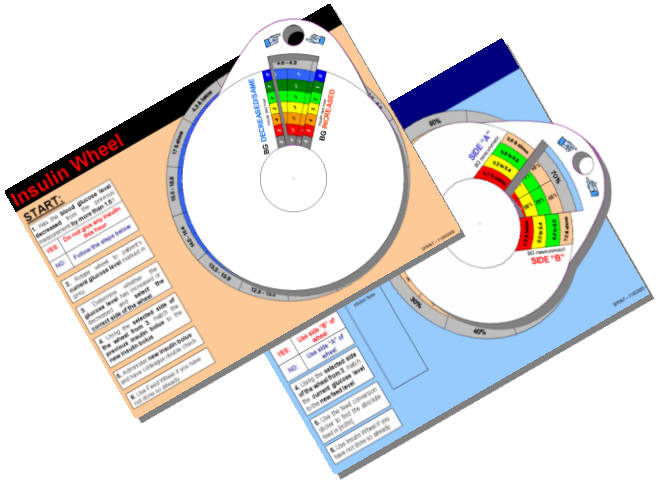
Department of Mechanical Engineering,
University of Canterbury
Christchurch, New Zealand

UC UNIVERSITY OF CANTERBURY
Te Whare Wānanga o Waitaha
CHRISTCHURCH NEW ZEALAND

Glycaemic control with SPRINT

Paper-based protocol that titrated treatments based on patient-specific response to insulin AND nutrition (insulin sensitivity)

- Reduced mortality 25-45%,
- Reduced organ failure (10%)
- Reduced cost per patient ($1000-2000)
- Halved hypoglycaemia!



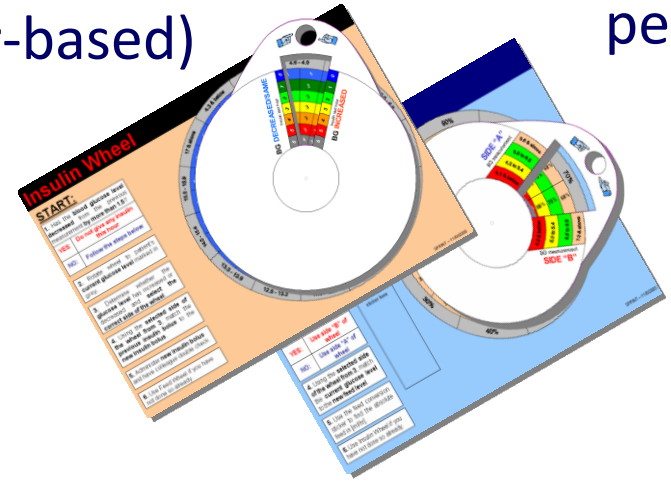
No other protocol directly accounted for insulin sensitivity.

UC BIOMEDICAL ENGINEERING

A New Glycaemic Control Paradigm

SPRINT (2006 – 2012)

- Virtual trials were used to create a dynamic sliding scale
- Hourly binned data extracted from ICU charts
- No data recorded while in use (paper-based)



STAR (2013 – present)

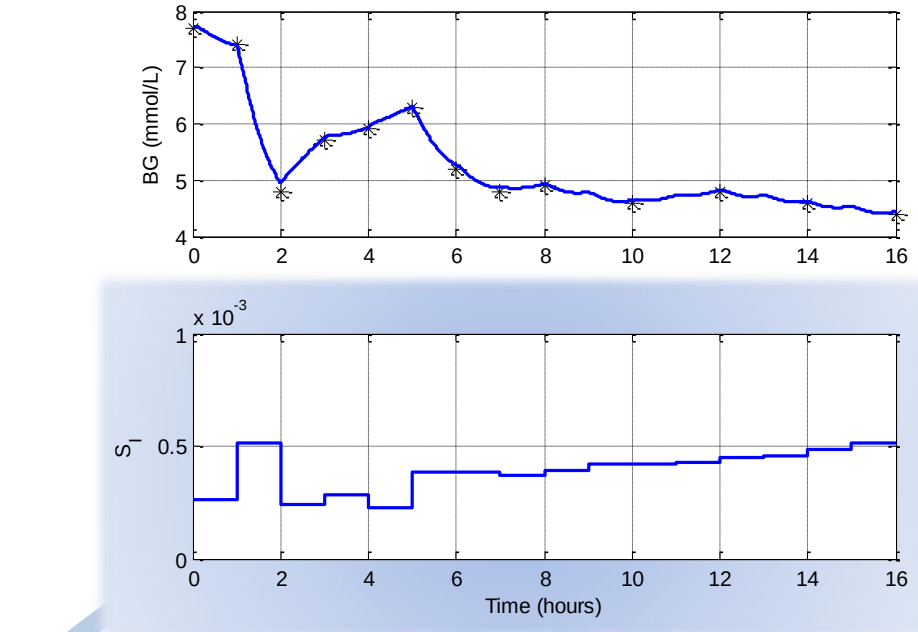
- Framework and logic developed using virtual trials, and SPRINT data…
- …. but high resolution data recorded during use, which could be used to improve performance.

UC BIOMEDICAL ENGINEERING

UC BIOMEDICAL ENGINEERING

SPRINT era parameter ID and prediction

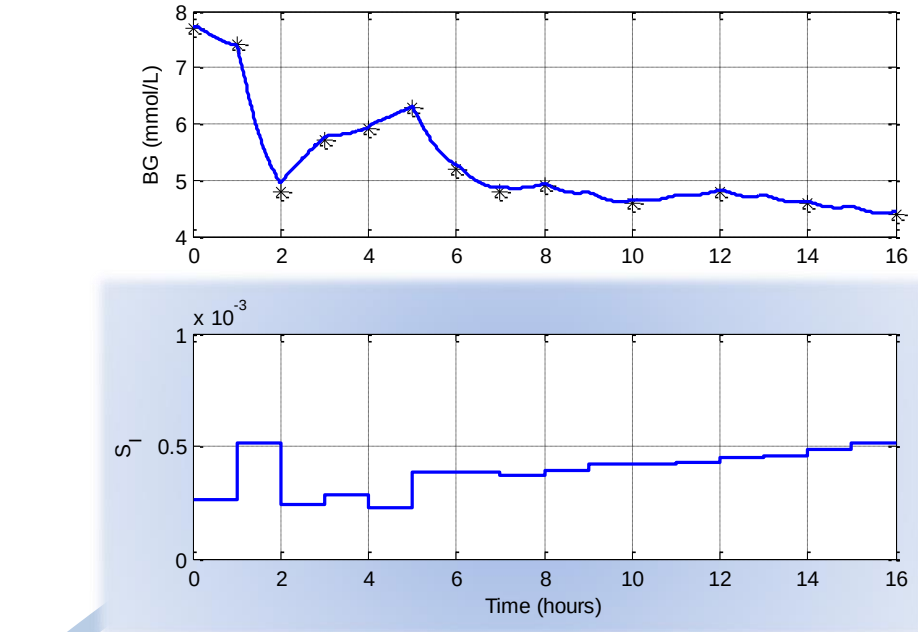
- The SI profile was recovered from BG, insulin, and nutrition data.
- Fitting methodology was developed for hourly binned data.
- The prediction framework requires an hourly SI value for forecasting.
- Hospital implementation has a data density that varies from 1 to 3+ hour measurement intervals.
- Intermediate BG values are resampled hourly using linear interpolation to address this issue.



UC BIOMEDICAL ENGINEERING

SPRINT era parameter ID and prediction

- The SI profile was recovered from BG, insulin, and nutrition data.
- Fitting methodology was developed for hourly binned data.
- The prediction framework requires an hourly SI value for forecasting.
- Hospital implementation has a data density that varies from 1 to 3+ hour measurement intervals.
- Intermediate BG values are resampled hourly using linear interpolation to address this issue.



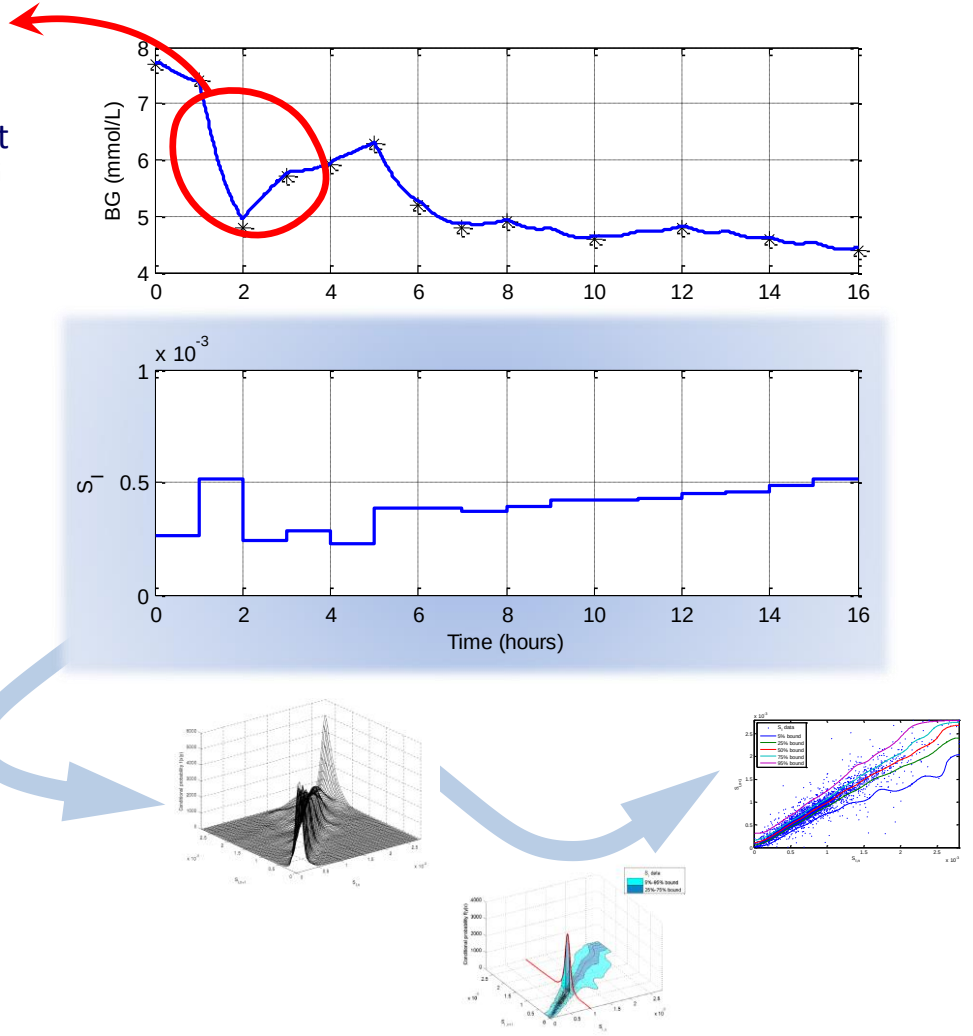
This approach worked well for SPRINT data, which was (by definition) in perfect hourly intervals. **What to do, if that's no longer true?**

If you enforce hourly SI:

- If a measurement isn't perfectly on the hour, and the data is resampled hourly, then large and silent fitting errors can occur **around highly variable BG**

- The data may fit the new, resampled measurement perfectly, but miss the actual one 10 minutes later!

This leads to artificial smoothing of the SI profile, and therefore virtual trial validity is reduced!



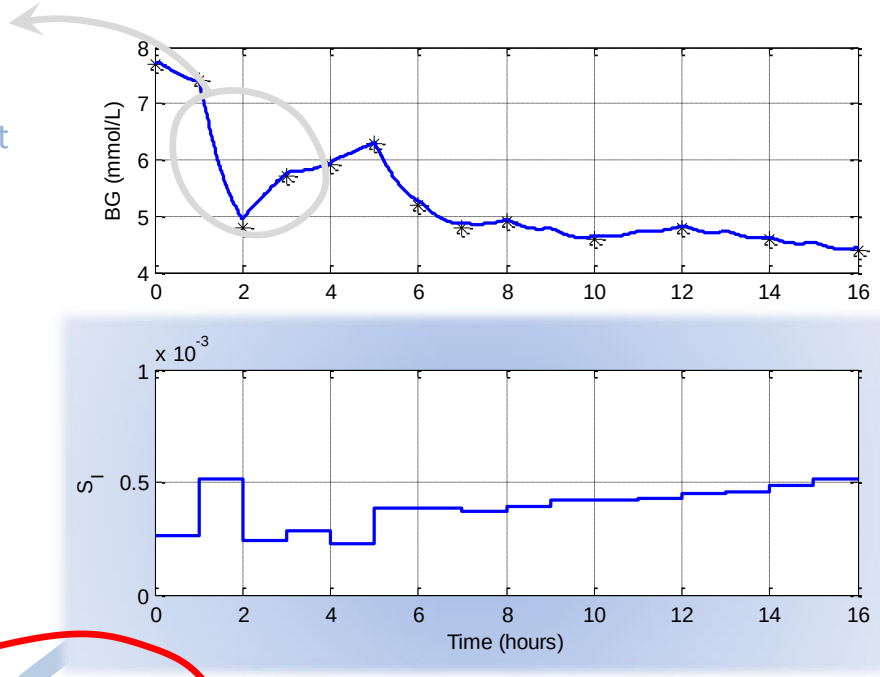
UC BIOMEDICAL ENGINEERING

If you enforce hourly SI:

- If a measurement isn't perfectly on the hour, and the data is resampled hourly, then large and silent fitting errors can occur **around highly variable BG**

- The data may fit the new, resampled measurement perfectly, but miss the actual one 10 minutes later!

This leads to artificial smoothing of the SI profile, and therefore virtual trial validity is reduced!

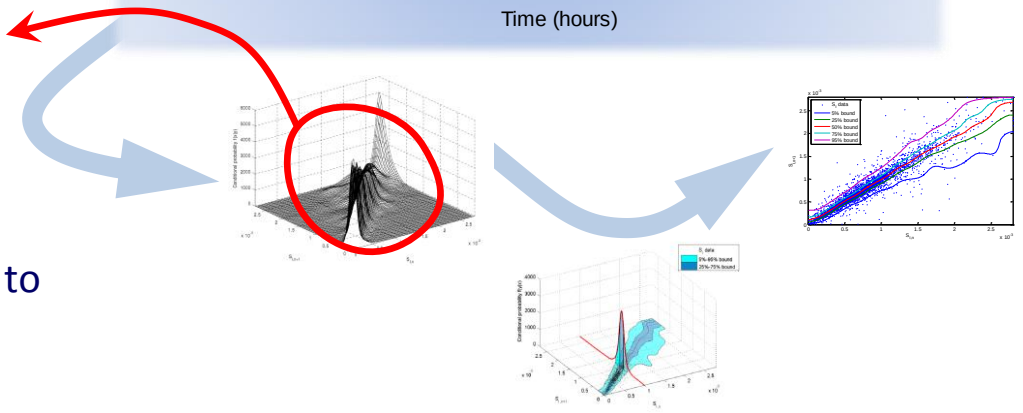


If you change the duration of SI "windows":

- The stochastic model was not built to handle different time intervals!

- To cope with this variable, you will need to add another dimension to the model.

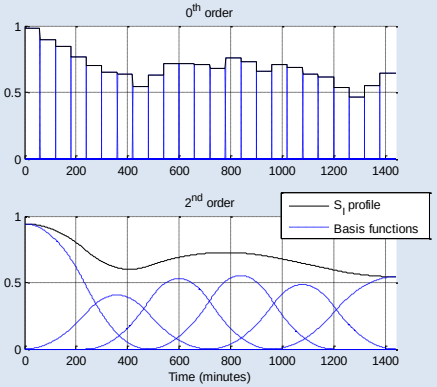
This means you run headlong into the curse of dimensionality!



Which leaves us with one major question:

HOW DO WE KEEP A REGULAR SI PROFILE IN THE FACE OF IRREGULAR DATA?

Change SI to a *b-Spline*



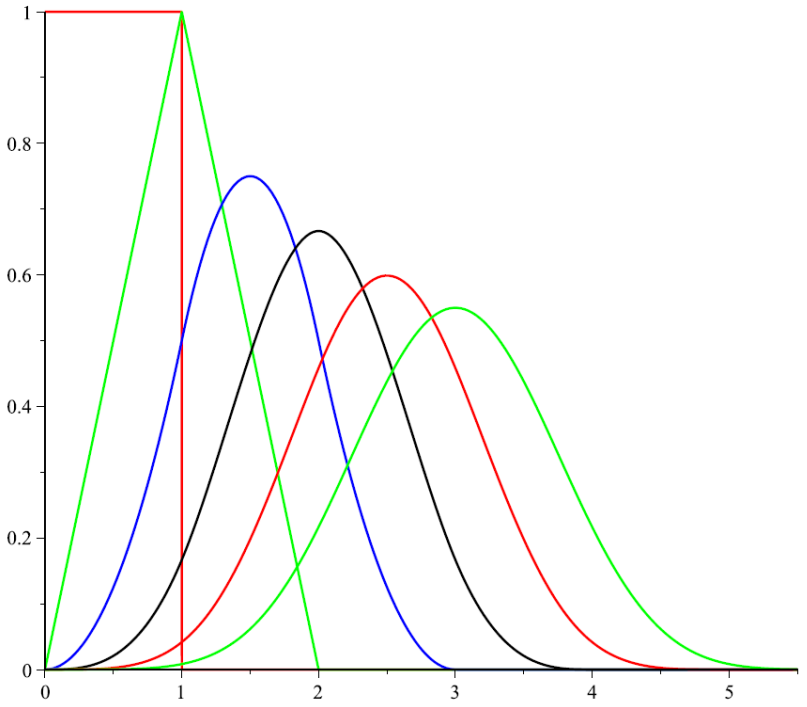
AND

Convert glucose model to a SDE

$$\dot{G} = \boldsymbol{G_x} + S_I f_1(G, Q) + f_2(G, P)$$

What is a *b-Spline* basis?

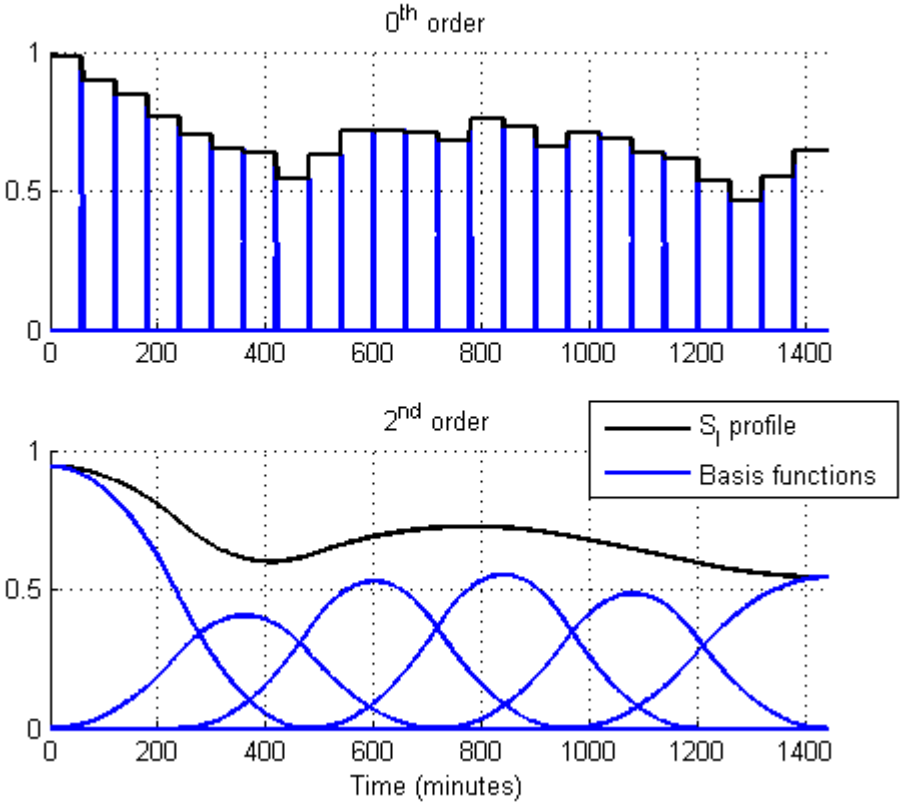
- A *b-Spline* is a piecewise polynomial of degree *n* that is described by control points, or knots
- As a spline, it is interesting in that it has minimal local support.
- The basis function is generated by linear combination of each constituent spline.
- Conveniently, this linear combination sums to unity at all points (prior to weighting individual splines to fit data).



UC BIOMEDICAL ENGINEERING

In our Context:

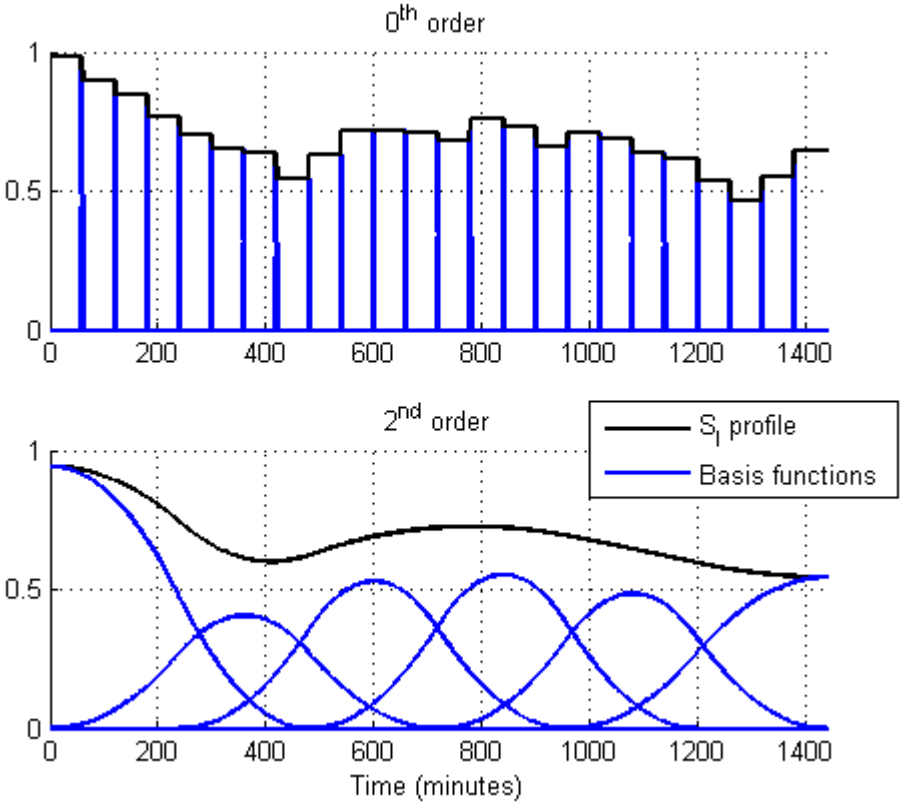
- An hourly SI profile is simply a 0th order *b-Spline* basis. Why not increase the order?
- Higher order basis functions have increased local support, which trades variance for bias.
- Major trends can be reproduced at the cost of high frequency changes.
- On a positive note, the degree of local support can remove the need for artificially increasing data density via linear interpolation



UC BIOMEDICAL ENGINEERING

In our Context:

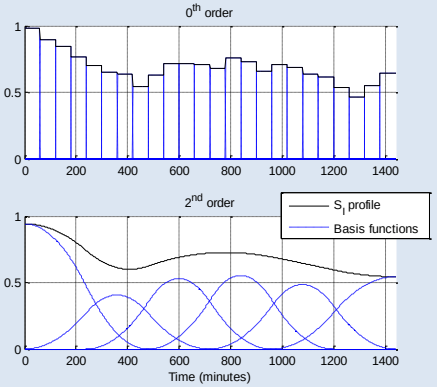
- An hourly SI profile is simply a 0th order *b-Spline* basis. Why not increase the order?
- Higher order basis functions have increased local support, which trades variance for bias.
- Major trends can be reproduced at the cost of high frequency changes.
- On a positive note, the degree of local support can remove the need for artificially increasing data density via linear interpolation



Regularising the SI profile using 2nd order b-Spline basis functions can eliminate the issue with timing error, **but introduces a new problem with high frequency BG variation!**

UC BIOMEDICAL ENGINEERING

Change SI to a *b-Spline*



AND

Convert glucose model to a SDE

$$\dot{G} = \boldsymbol{G_x} + S_I f_1(G, Q) + f_2(G, P)$$

The World's Most Basic SDE!

The other half of the picture:

- Introduce a "process noise" term into the glucose equation
- Use this new parameter to capture the variation in BG that cannot be explained using the new, regularised SI profile
- Instead of borrowing from the *extremely* computationally expensive SDE theory, why not simply call Gx the "**average process noise over the measurement interval**"?

$$\dot{G} = \mathbf{G}_x + S_I f_1(G, Q) + f_2(G, P)$$

The World's Most Basic SDE!

The other half of the picture:

- Introduce a "process noise" term into the glucose equation
- Use this new parameter to capture the variation in BG that cannot be explained using the new, regularised SI profile
- Instead of borrowing from the *extremely* computationally expensive SDE theory, why not simply call Gx the "**average process noise over the measurement interval**"?

$$\dot{G} = \mathbf{G_x} + S_I f_1(G, Q) + f_2(G, P)$$

Uh, that's nice and all, but you know you still have to actually fit that parameter, right?

UC BIOMEDICAL ENGINEERING

Fitting the World's Most Basic SDE!

Leverage the definition of a *b-Spline*:

- The basis must sum to 1 at all times, and the definition of the noise term is zero mean.
- Why not say the noise term must be **zero mean across the duration of every individual function**?
- The Gx values are all weighted according to the local value of each constituent spline.
- Zero mean is now enforced for every constituent function, and suddenly the system is full rank.

$$\dot{G} = \mathbf{G}_x + S_1 f_1(G, Q) + f_2(G, P)$$

Fitting the World's Most Basic SDE!

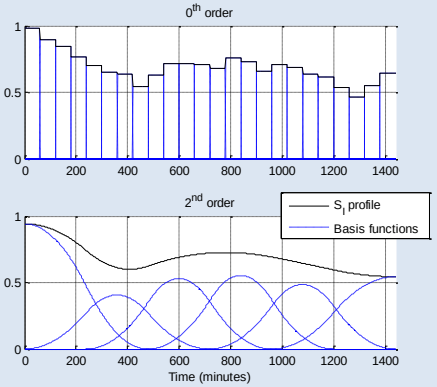
Leverage the definition of a *b-Spline*:

- The basis must sum to 1 at all times, and the definition of the noise term is zero mean.
- Why not say the noise term must be **zero mean across the duration of every individual function**?
- The Gx values are all weighted according to the local value of each constituent spline.
- Zero mean is now enforced for every constituent function, and suddenly the system is full rank.

$$\dot{G} = \mathbf{G}_x + S_1 f_1(G, Q) + f_2(G, P)$$

Great!

Change SI to a *b-Spline*



- SI profile now robust to irregular timing
- G_x represents an 'average effect'

AND

Convert glucose model to a SDE

$$\dot{G} = \boldsymbol{G_x} + S_I f_1(G, Q) + f_2(G, P)$$

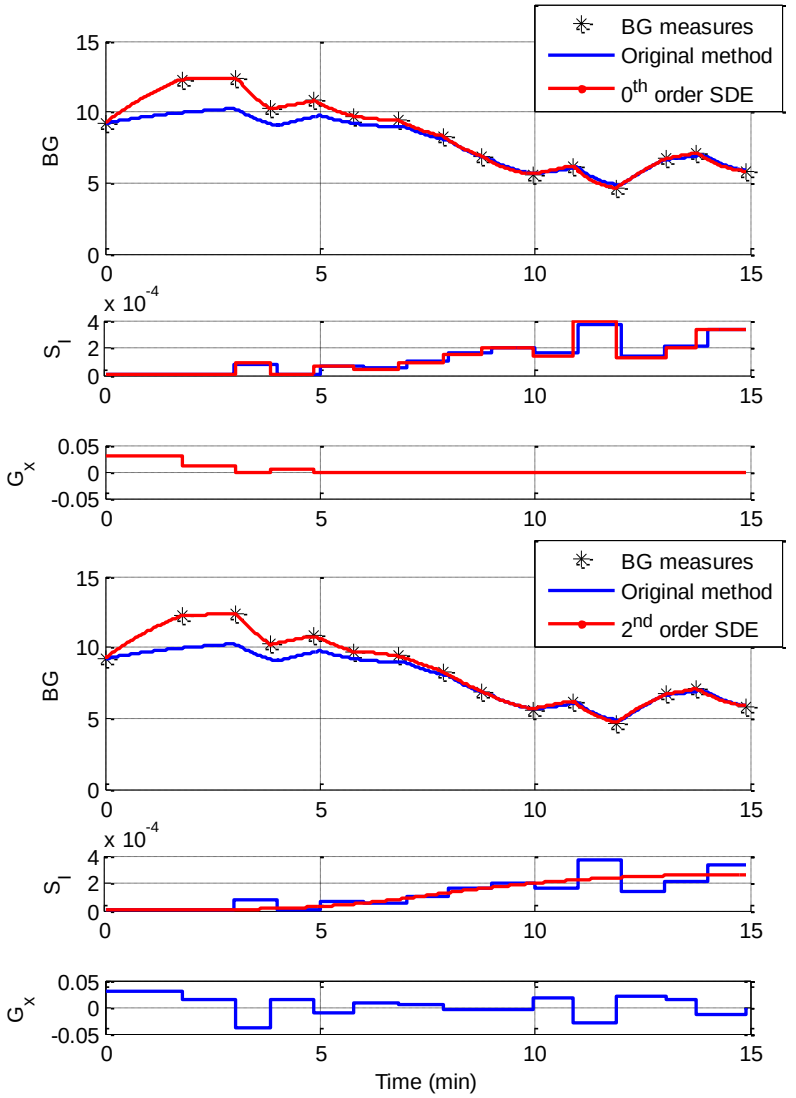
An Example or Two

A single patient has been fitted with:

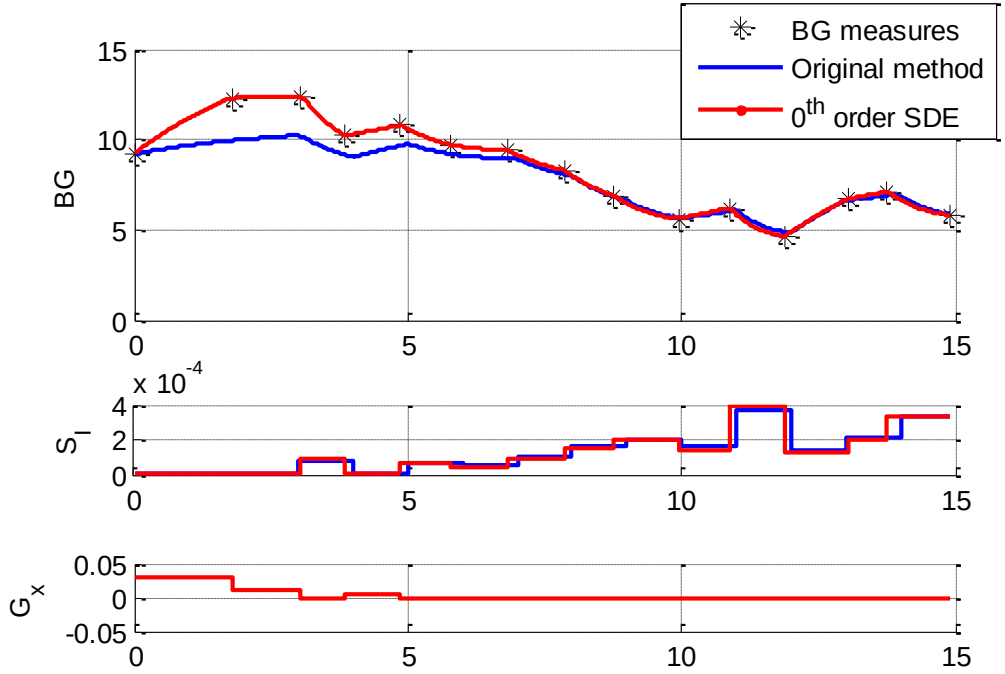
1) Original method

2) 0^{th} order *b-Spline* + SDE

3) 2^{nd} order *b-Spline* + SDE



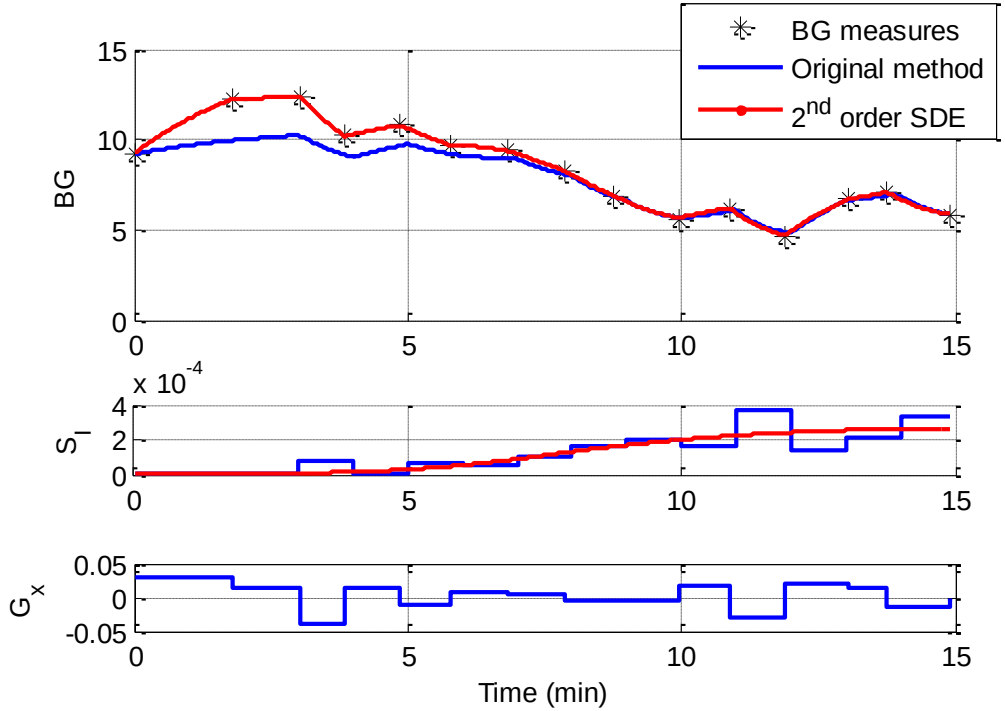
UC BIOMEDICAL ENGINEERING



Original method vs. 0th order SDE

In short, the zero mean constraints enforce Gx = 0 at all points except where SI cannot account for the BG variation.

The resulting affect on SI is therefore negligible.



Original method vs. 2th order SDE

High frequency fluctuations in SI are damped by new profile.

The remaining variation in BG is captured by Gx, hence greater Gx variability.

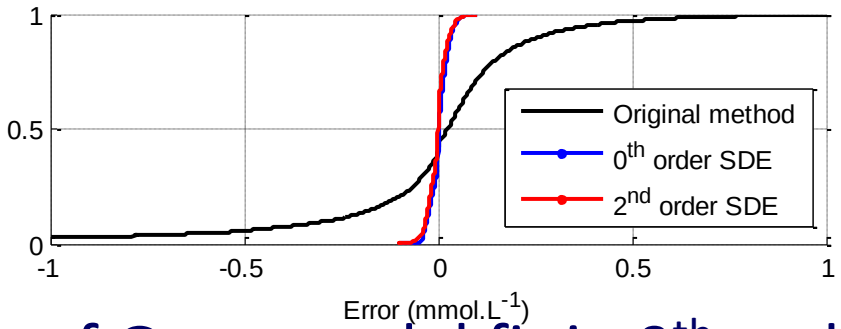
Summary

- New method ensures model will always fit the data.
- Over-fitting is avoided by forcing SI to account for long-term changes in BG, and Gx to account for short term changes.
- Virtual trials can now reproduce the original results despite irregular data, and are thus more valid.

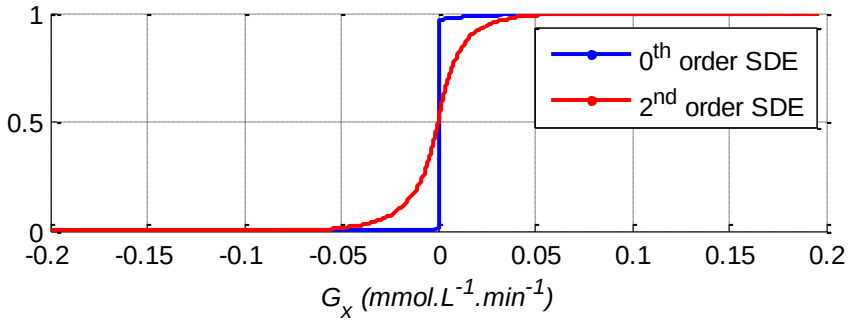
UC BIOMEDICAL ENGINEERING

Cohort results

- BG fitting error after fitting across the entire STAR cohort (~12,000 hours of patient data):



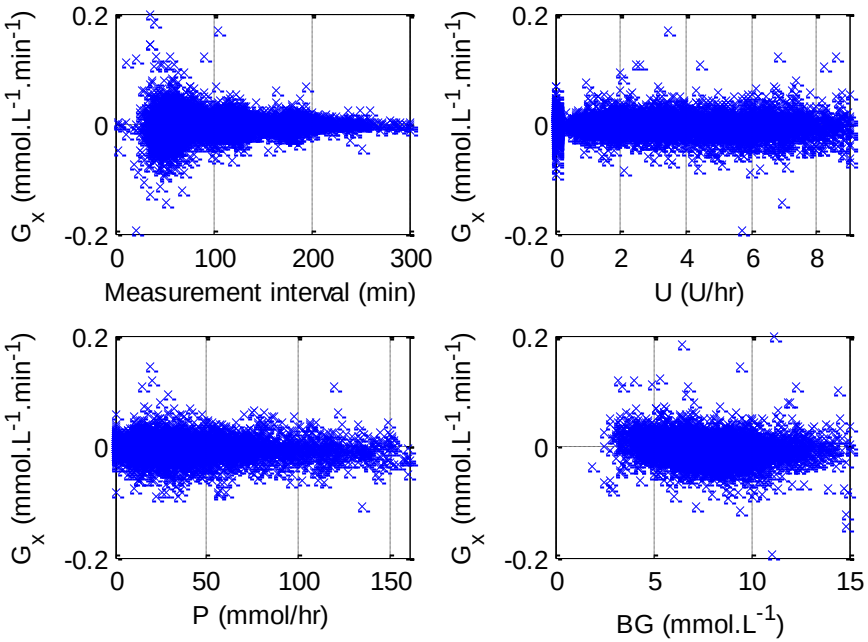
- Contribution of Gx to model fit in 0^{th} and 2^{nd} order versions



UC BIOMEDICAL ENGINEERING

An interesting overview

- A plot of fitted Gx values vs local conditions:



- Gx is not being obviously biased by anything other than measurement interval (due to definition).
- SI can capture changes similarly regardless of average exogenous insulin, nutrition, or current BG.

UC BIOMEDICAL ENGINEERING

Conclusions

- A new methodology for directly balancing “physiological changes” and “noise”.
- Robust, and avoids the computation problems of SDEs.
- Much better suited to irregular data, as gathered by STAR, and preserves the validity of virtual trials going forward.

UC BIOMEDICAL ENGINEERING

Acknowledgement

This work was supported by EU FP7 IRSES (FP7-PEOPLE-2012-IRSES) program, project title: eTime - Engineering Technology-based Innovation in Medicine, Grant No. 318943.

Questions?