Mapping the differences between pancreatic Beta cell models

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Introduction

Beta cells are cells in the pancreas which create and release insulin. Numerical models of Beta cells have been developed to aid in the understanding of diabetes. Various inputs to these models can greatly impact the resulting dynamics, causing very different regimes of behaviour to emerge.

Our goal is to find the differences between the different Beta cell models that exist. These Beta cell models take time to run, as such we build fast statistical surrogate models (emulators) to help us gain information about the models.

Emulation Strategy

We want to build a classification emulator; i.e. a statistical model that can predict which regime a Beta cell model would output for a new set of input parameters.

There are many off-the-shelf choices for a classification emulator. One such example is a RobustMax classifier[1,2]. Here, each regime is given it's own Gaussian Process (for simplicity, i.e. a wiggly line). For any input point value, the regime Gaussian Process (GP) with the largest value is which regime the classifier predicts.
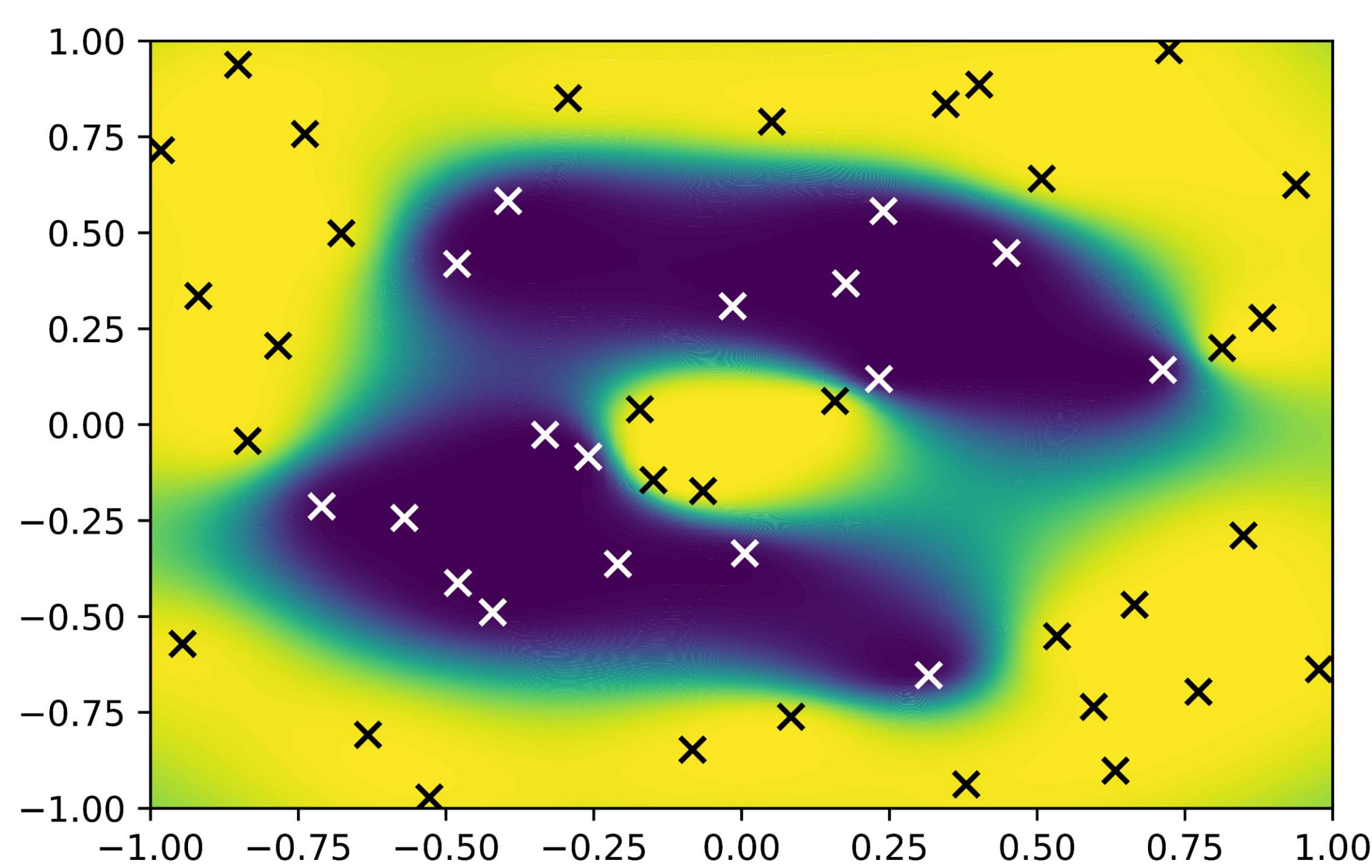

Figure 1: An example prediction from a RobustMax classifier. The colour indicates the prediction probability: full yellow equates to 100% confidence the simulator is in regime 1 whereas full blue equates to 100% confidence the simulator is in regime 2. The crosses indicate the training simulations used to build this classifier.

Zooming in:

Some of the regions are very rare, and so an initial training data ensemble might not include some of the rare regimes. We might then, incorrectly, conclude that one Beta cell model is incapable of producing said regime.

Our solution to this, is to build these classifier emulators iteratively. We first build an emulator for separating regime 1 from "all other regimes". We then use this classifier to choose a new batch of simulations, targeting simulations within "all other regimes", which should yield more of the rarer regimes.
This process can then be repeated. We separate regime 2 from all other remaining regimes, then we separate regime 3, and so on.
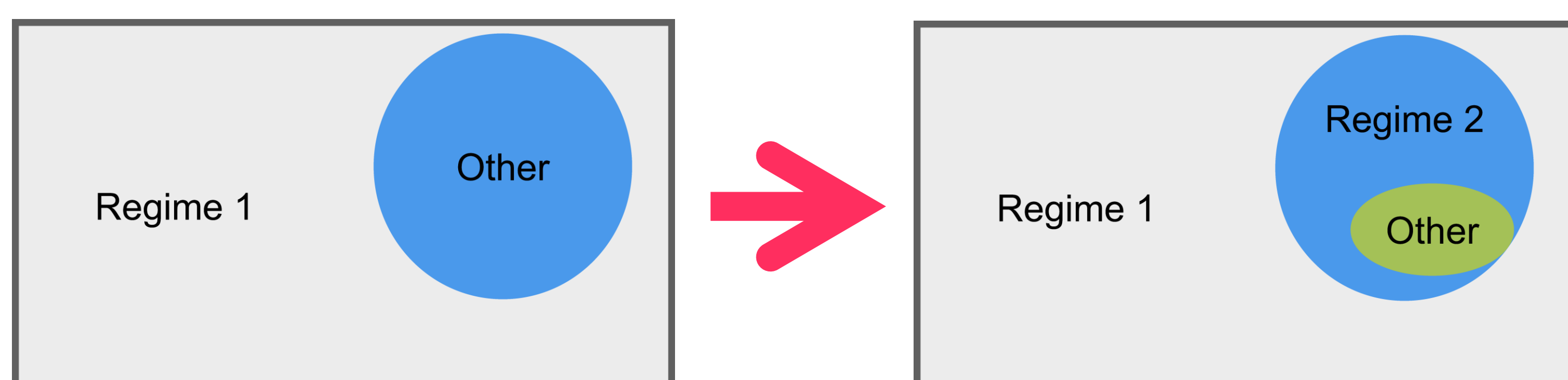

Figure 2: A representation of the zooming in strategy

Results

We apply our strategy to two different Beta cell models[3,4], starting with 200 initial simulations, and adding 200 extra simulations in each round of zooming in.

With this, we can generate plots like the following, which attempt to summarise the predicted regimes in higher dimensions.
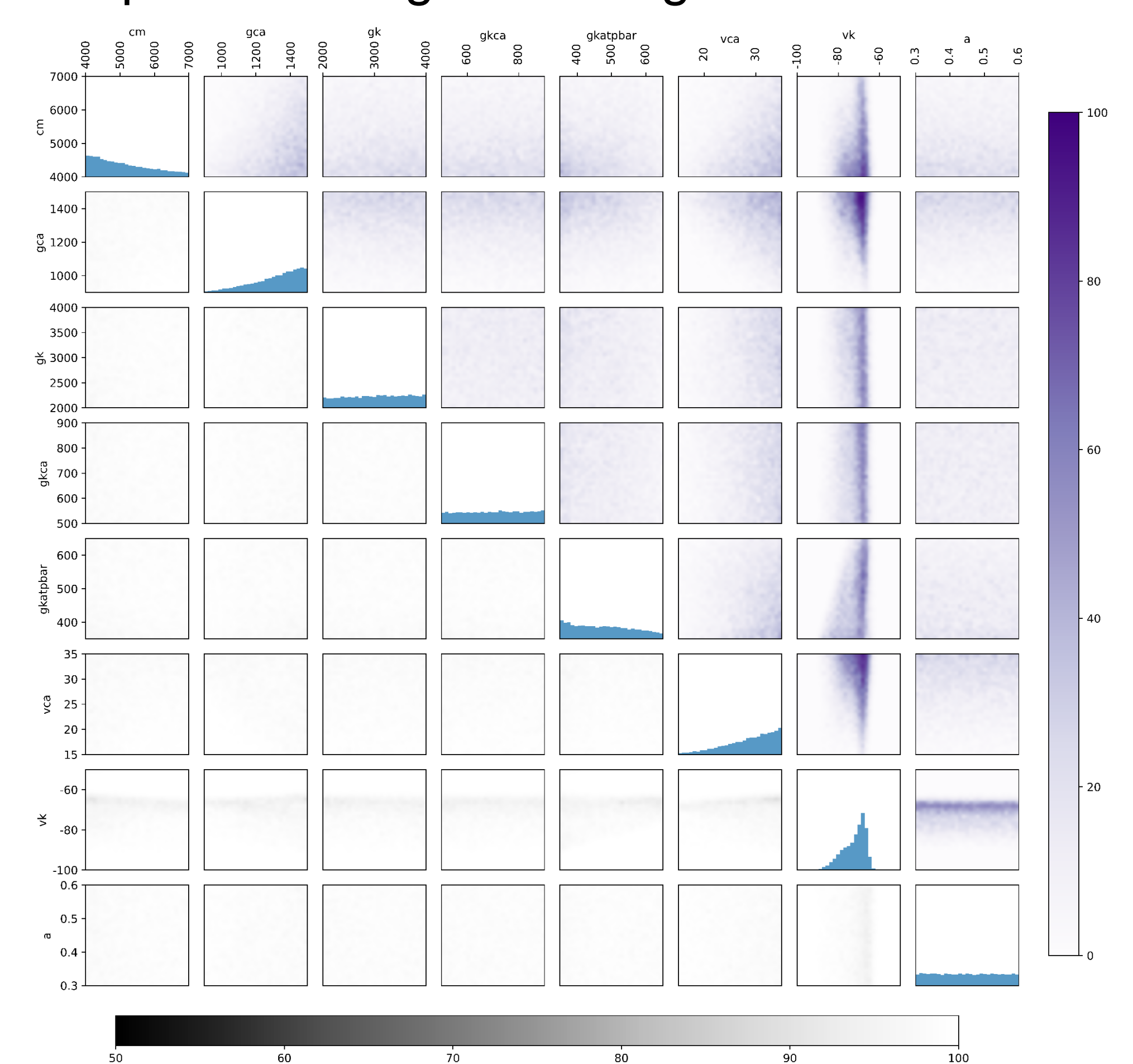

Figure 3: A set of plots summarising where the emulator for the Biophan model believes "tonic-spiking" regimes are. The upper right plots show this in 2D slices, the diagonal in 1d slices, and the bottom left shows representations of the uncertainty.

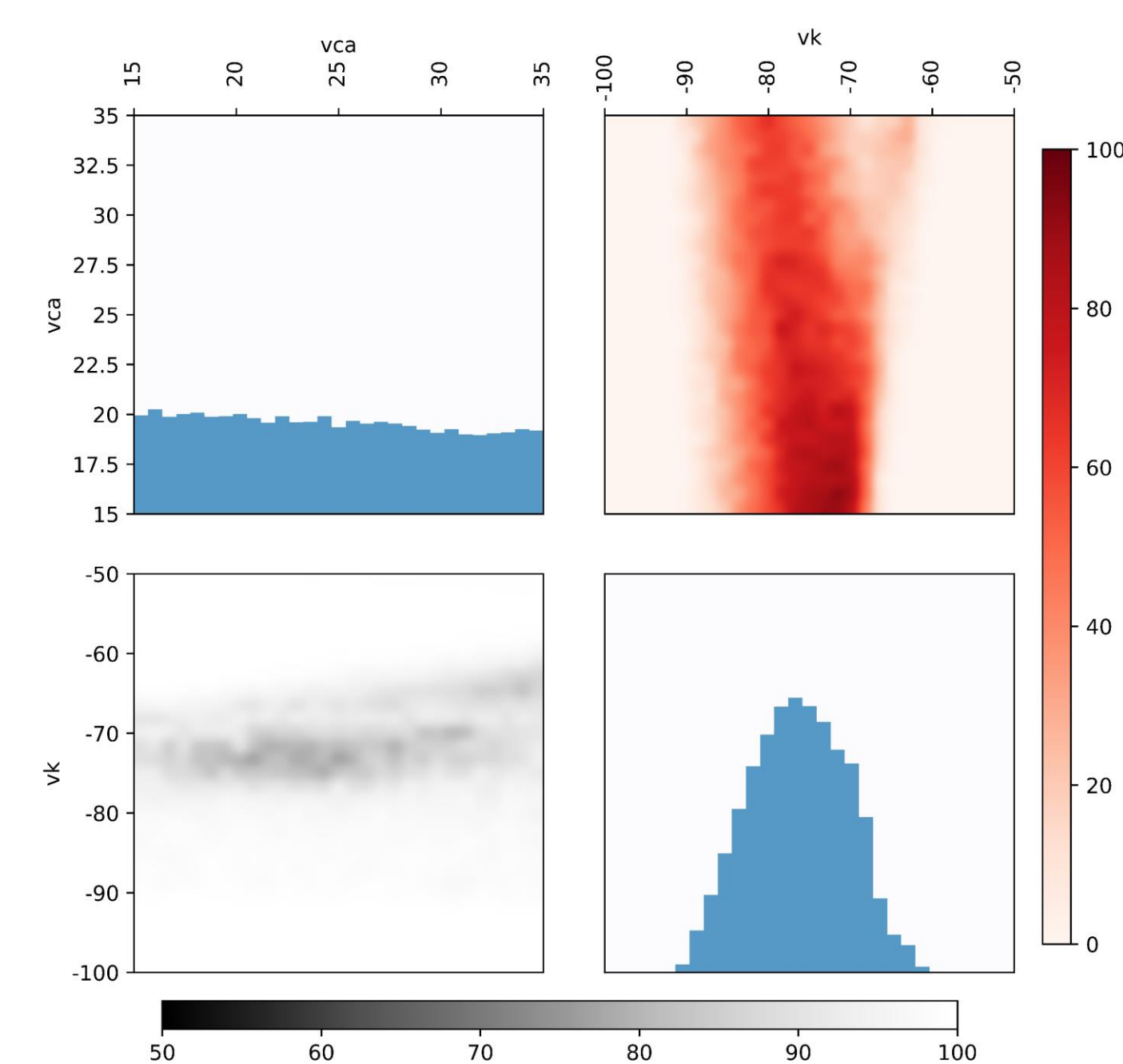We can also use these emulators to map where the two emulators disagree:

Figure 4: A set of plots showing where the CK model and the Biophan model disagree.

Going Forward

We have managed to build emulators which can find and map very small regimes. This allows us to zoom in and compare the differences between two different Beta cell models. Going forward, we want to extend this to more Beta cell models, in higher dimensions, and to perform more comparisons.

References:
[1] Hernández-Lobato, Daniel, Jose Hernández-lobato, and Pierre Dupont. "Robust multi-class Gaussian process classification." Advances in neural information processing systems 24 (2011).
[2] Matthews, Alexander G. de G., et al. "GPflow: A Gaussian Process Library using TensorFlow." J. Mach. Learn. Res. 18.40 (2017): 1-6.
[3] Chay, Teresa Ree, and Joel Keizer. "Minimal model for membrane oscillations in the pancreatic beta-cell." Biophysical journal 42.2 (1983): 181-189.
[4] Bertram, Richard, and Arthur Sherman. "A calcium-based phantom bursting model for pancreatic islets." Bulletin of mathematical biology 66.5 (2004): 1313-1344.

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