Poster Presentation Abstract, The 7th International Conference on Systems Biology, Yokohama Japan, 9-11 October 2006 (ICSB-2006)

Study of Dependency of Synchronization of Beta-cells Insulin Secretion on Size of Langerhans Islets

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The simulations of intra-cellular processes such as metabolic networks or gene expression control mechanisms have been widely covered in many tools available today[1, 2] however the simulation of multiple cells interacting in a common environment such as tissues is not yet fully available.

Tsim (Tissue Simulator) was initially developed for the study of early growth of tumours inspired on works previously done in the area but unlike these studies, the simulation process in Tsim happens both inside and outside the cells.

The regulation of glucose in blood is achieved by glucose sensing cells named beta-cells located in human pancreas, their function is to secrete insulin to signal to muscle and liver they should capture glucose from blood and convert it to glycogen.

This signaling is composed of pulses that are synchronized among the cells within the islets of Langerhans. In this study we propose that there's a lower and upper limit for the size of these clusters so their synchronization and response time will comply with the time constants of human body.

In order to quantify these dimensions, hybrid automata simulation models were created in Tsim with cells disposed in a spatial array as proposed in literature[4] and glycolysis and insulin secretion mechanisms were simulated using the kinetic equations from previous studies[3]. This model is based on a 2-dimensional array of cells, blood vessels and extra-cellular matrix space as well as on differential equations for diffusion of inter-cellular species and intra-cellular metabolism kinetics.

The final results were compared to data obtained by other mathematical models based on deterministic equations[5] and in vivo data in order to evaluate the consistency of this study.

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Insulin Secretion Mechanism (1)

- Insulin is a hormone secreted by pancreas when the levels of glucose in blood reach a upper limit;
- Insulin promotes the conversion of glucose to glycogen inside muscle and liver cells;
- Most insulin is secreted by Beta-cells within the pancreas;
- Beta-cells are arranged into structures called "Langerhans Islets".

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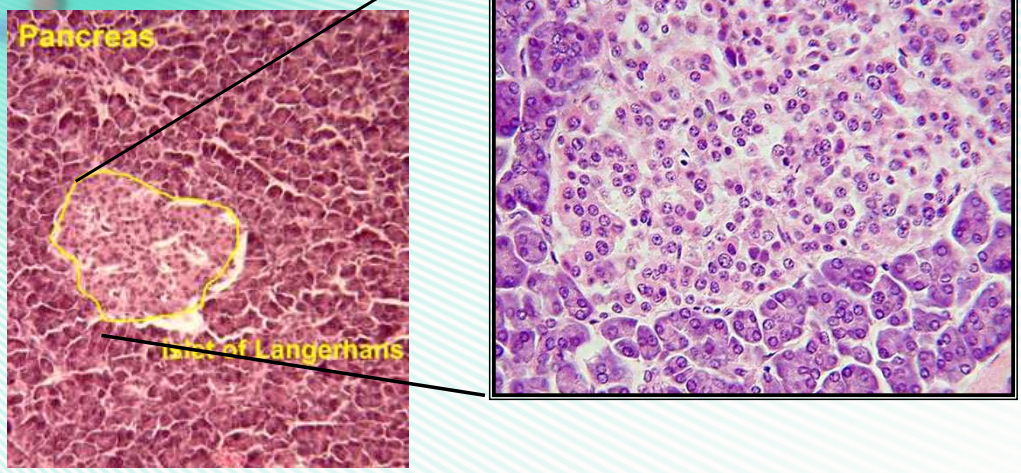
Insulin Secretion Mechanism (1)

- There are about one million islets in a healthy adult human pancreas, which are interspersed evenly throughout the organ;
- Each islet is 50-500 μm in diameter and contains ~1,000 cells:
  - Insulin-producing Beta cells (65-80% of the islet cells)
  - Glucagon-releasing alpha cells (15-20%)
  - Somatostatin-producing delta cells (3-10%)
  - Pancreatic polypeptide-containing PP cells (1%)

Islet of Langerhans



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Insulin Secretion Mechanism (2)

- Beta-cells secrete insulin in pulses. These pulses are synchronized within the islets and among the islets in pancreas;
- The proper functioning of glucose-sensing/insulin-secretion mechanism depends on synchronized secretion of pancreatic islets;
- Bertram et al* propose two mechanisms for synchronization:
  - Electric coupling of cell membranes within islets;
  - Glucose level oscillation feedback among islets;

***Bertram R et al. Intra- and Inter-islet synchronization of metabolically driven insulin secretion. Biophys J. 89(1), 107-19 (2005)**

Islet of Langerhans: Ideal for 3D Tissue Modeling !

- Due to the (i) limited number of cells per Islet, and (ii) extent of knowledge regarding its anatomy and biology; Langerhans Islets are ideal targets for computational 3D Tissue modeling
- Our starting point:
  - It is known that chronic overweight as well as pregnancy lead to increase in size of islets;
  - Transplantation of islets eventually lead to loss of cells in islet□s outer limits, leading to impairment of its functioning;

□Does Islets functioning (synchronization) depend on its size (number of cells) or distribution of vessels?□

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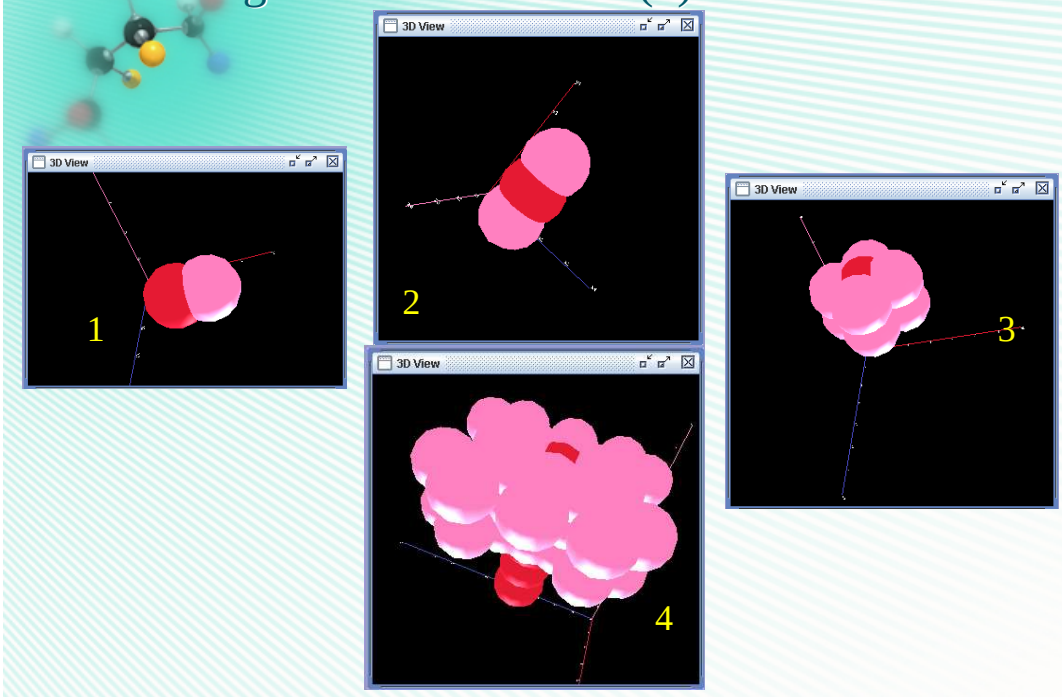
Aims and Methods

- This work proposes to investigate the effects of both the:
  - **number of Beta-cells per islet, and**
  - **proportion of blood vessels,**

  on blood glucose sensing/metabolization by Langerhans Islets;

- To address this question, we developed and simulated four different Langerhans Islet models using our 3D-Tissue Simulator (TSim) software:
  - One Beta-cell and one blood vessel access;
  - Two Beta-cells and one blood vessel access;
  - 8 Beta-cells around two blood vessel accesses;
  - 48 Beta-cells around 5 blood vessel accesses;

Langerhans Islet Model (1)



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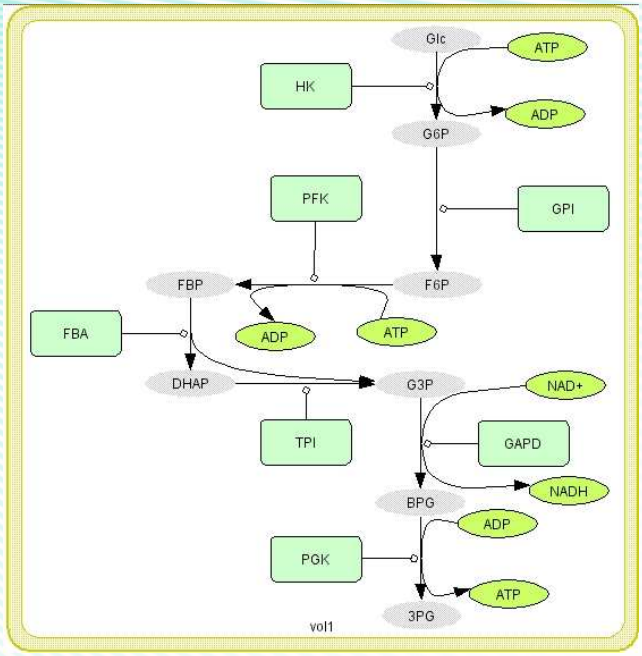
Langerhans Islet Model (2)

- These models use the glycolytic equations from our previous work (Genet Mol Res 5(3):525-535, 2006);
- Insulin secretion is coupled to glycolysis intermediary FBP concentration;
- The high-frequency bursts due to electrical activity of cell membrane were not considered;



Model Analysis

- The values measured in this study were:
  - Glucose maximum and minimum concentration in blood;
  - Peak concentration of insulin in blood;
  - Time to first pulse of insulin (edge) in blood;
  - Period between to insulin pulses (peak) in blood;
  - Lag between peak of FBP and insulin in cell neighborhood (peak);

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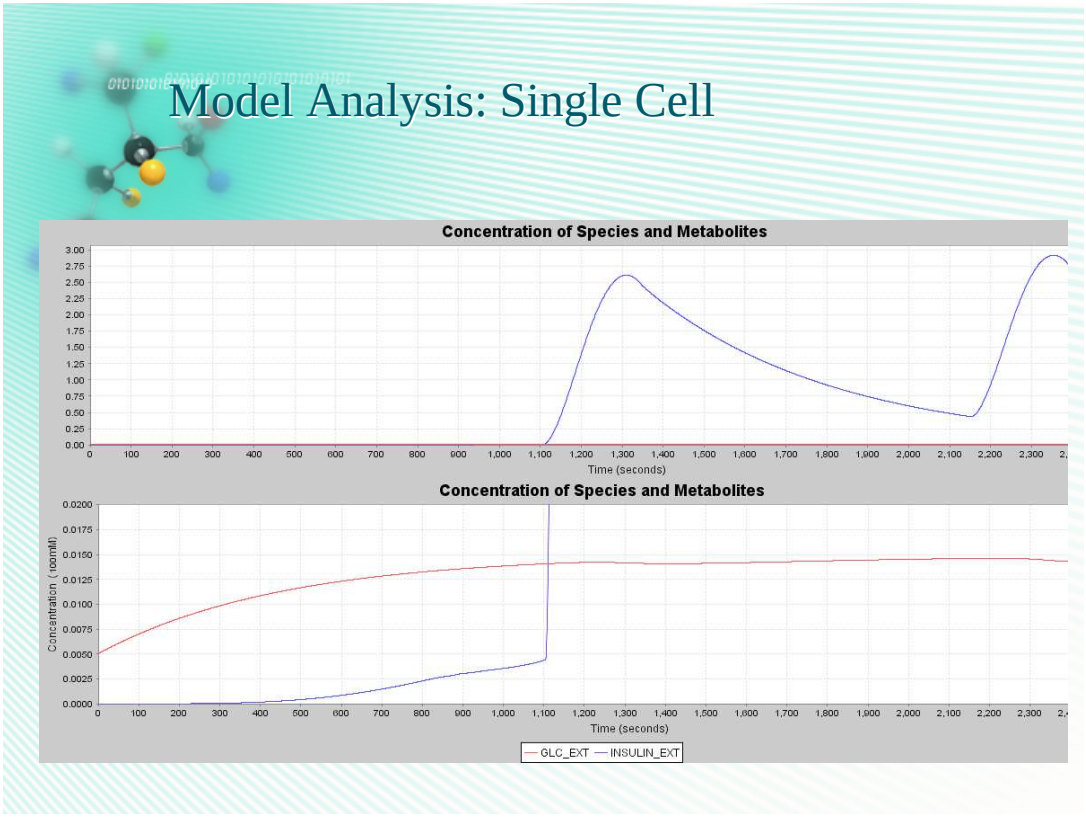

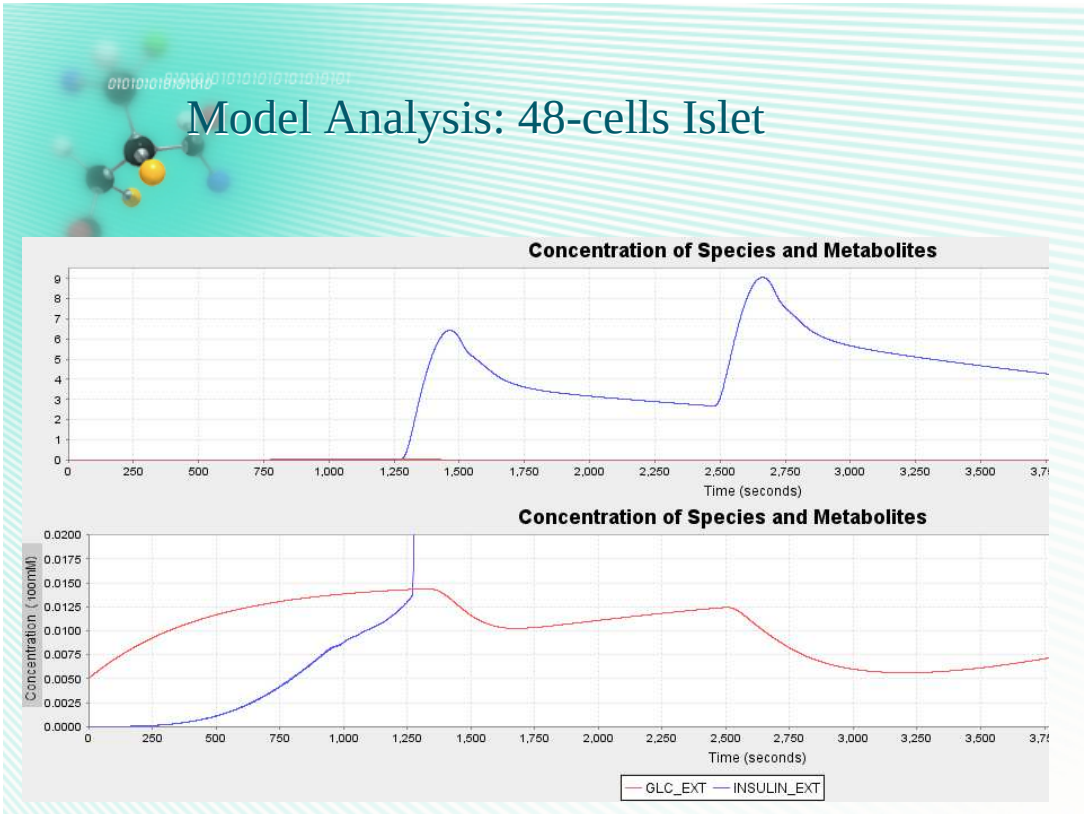

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Ongoing Results

- Glucose concentration varies more in big islets than in small ones since the production of insulin is higher:
  - Big islets could cause overshoot in blood glucose concentration (max 1.25mM- min 0.05mM);
  - Small islets have a smoother effect on blood glucose, being almost ineffective (max 1.5mM- min 1.4mM);
- The concentration of insulin in blood accesses in bigger islets tends to decrease more slowly due to the in diffusion of insulin stored in the islet environment flowing into blood:
  - Smaller islets tend to have narrower insulin pulses;
  - Bigger islets tend to have wider insulin pulses;

Preliminary Conclusions

- The number of Beta-Cells on an islet and its proportion to blood vessels will influence on how it will respond to glucose levels either by overshooting glucose concentrations or by being a damped controller;
- When modeling tissues it is necessary to consider the diffusion speed of the species since this delay may induce control issues;

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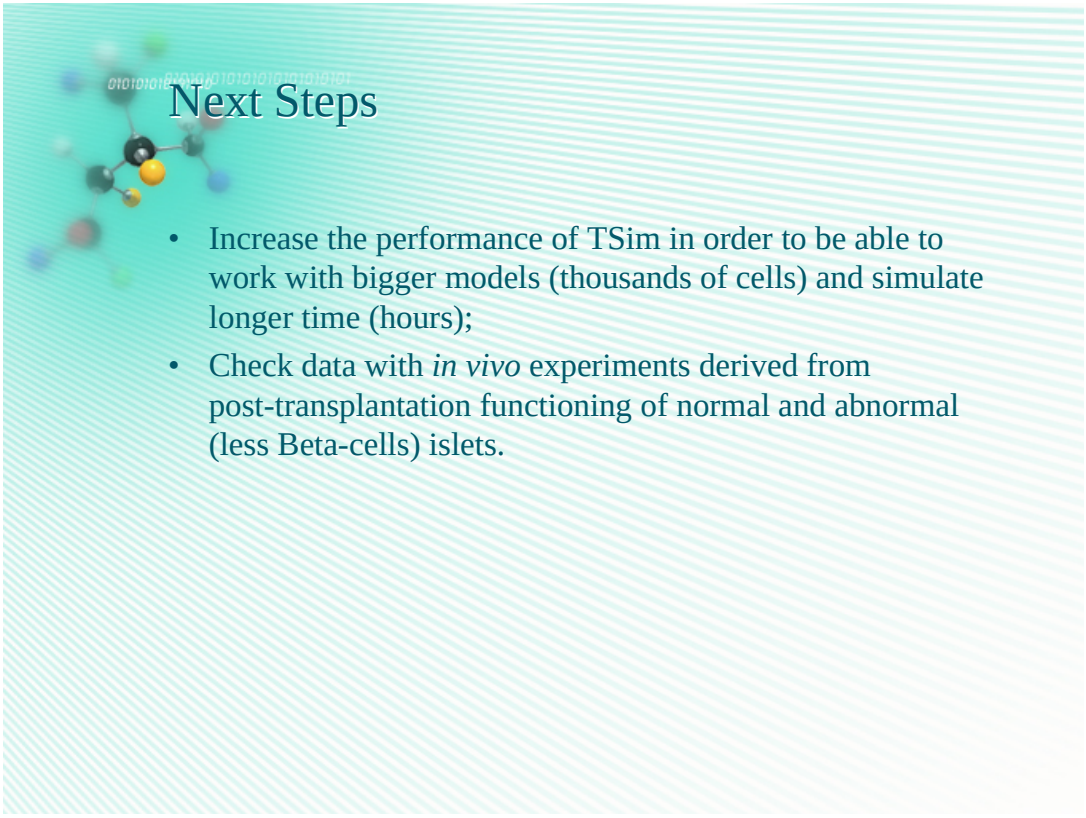

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