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Dynamical Modelling of the effect of Insulin-like Growth Factor 1 on Human Cell Growth

A thesis presented in fulfilment of the requirements for the degree of

Master of Science
in Mathematics
at Massey University, Albany, New Zealand

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2013
Abstract

Insulin-like Growth Factor-1 (IGF-1) plays a vital role in human growth and development. Interactions with IGF-1 receptors and IGF-1 binding proteins (IGFBPs) regulate IGF-1 function. Boroujerdi et al. (1997) published a mathematical model describing dynamic regulation of IGF-1. We extended the Boroujerdi et al. (1997) model to evaluate the role of cyclic Gly-Pro (CGP) in dynamic regulation of IGF-1 function. Recent research from the Liggins Institute suggests that a metabolite of IGF-1, CGP, may have a role in regulating IGF-1 homeostasis, possibly through competitive binding to IGFBPs.

The goal of the research was to understand the kinetics of IGF-1, IGFBPs and CGP, along with their interactions with IGF-1 receptors. This goal and an understanding of how the kinetics mediate IGF-1 function was achieved through consideration of the nonlinear dynamics of the physiology using a modelling approach.

The resulting models were directly focused on three central theories. The first is that CGP can either inhibit, stimulate or maintain IGF-1 function based on the extent of receptor binding. The other theories are that CGP regulates IGF-1 through competitive binding to IGFBPs and that CGP does not directly interact with the IGF-1 receptors.

Four in vitro models were developed and fitted to experimental data. These included two implicit models which relied on two feedback terms in the equations. The second model was an alteration of the first to produce a reduction in cell number levels for high doses of CGP added to the system. The other two models were explicit models, the first of which could not express the IGF-1 dynamics well (it showed no CGP response). Although the models incorporated these theories, there are other mechanisms influencing the system which will have an effect on the data. Therefore the fourth model was introduced as a simplified version of the third. This was aimed at resembling cell culture situations more closely and was designed to have the receptor bound IGF-1 dependent on IGF-1 and CGP production rates.

The models can be used to predict cellular response in an in vitro situation, or as a basis for further research in this field.
Acknowledgements

I would like to thank my supervisors, Professor Graeme Wake and Dr Paul Shorten for their constant advice, encouragement and support throughout this project.

Prof. Wake and Dr. Shorten were funded to supervise this thesis via the Gravida National Centre for Growth and Development.

Thank you to Dr Jian Guan (Head Biologist at Liggins Institute) for her feedback, guidance and biological explanations.

In addition I would like to express my gratitude towards Mr Tony Pleasants and the Norman F Barry Foundation, Wake’s Scientific Consulting and Dr Guan the head of Neuroscience from Liggins Institute (Ministry of Business and Employment, MIBIE) for funding this project.

Lastly I would like to express my appreciation to my family, Alistair Watt, and his family for their understanding, love and support.
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<tr>
<td>BSA</td>
<td>Bovine serum albumin</td>
</tr>
<tr>
<td>CGP</td>
<td>Cyclo-glycyl-proline or Cyclic Gly-Pro</td>
</tr>
<tr>
<td>DE</td>
<td>Differential equation</td>
</tr>
<tr>
<td>DKP</td>
<td>Diketopiperazine</td>
</tr>
<tr>
<td>EDTA</td>
<td>Ethylenediaminetetraacetic acid</td>
</tr>
<tr>
<td>GPE</td>
<td>Glycine-proline-glutamate</td>
</tr>
<tr>
<td>IGF-1</td>
<td>Insulin-like Growth Factor 1</td>
</tr>
<tr>
<td>IGF-1R</td>
<td>Insulin-like Growth Factor 1 Receptor</td>
</tr>
<tr>
<td>IGFBP</td>
<td>Insulin-like Growth Factor Binding Proteins</td>
</tr>
<tr>
<td>kDa</td>
<td>Kilo Dalton (Dalton is a unit of mass based on molecular mass)</td>
</tr>
<tr>
<td>nM</td>
<td>nmol $L^{-1}$</td>
</tr>
<tr>
<td>ODE</td>
<td>Ordinary Differential Equation</td>
</tr>
<tr>
<td>PBS</td>
<td>Phosphate Buffered Solution</td>
</tr>
<tr>
<td>PDE</td>
<td>Partial Differential Equation</td>
</tr>
<tr>
<td>RK4</td>
<td>Runge Kutta fourth order method</td>
</tr>
<tr>
<td>SDS</td>
<td>Sodium Dodecyl Sulfate</td>
</tr>
<tr>
<td>SSE</td>
<td>Sum of Squares of Errors</td>
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<td>WST-1</td>
<td>Water Soluble Tetrazolium Salt-1</td>
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