

# Mathematical Modelling of Fat Metabolism

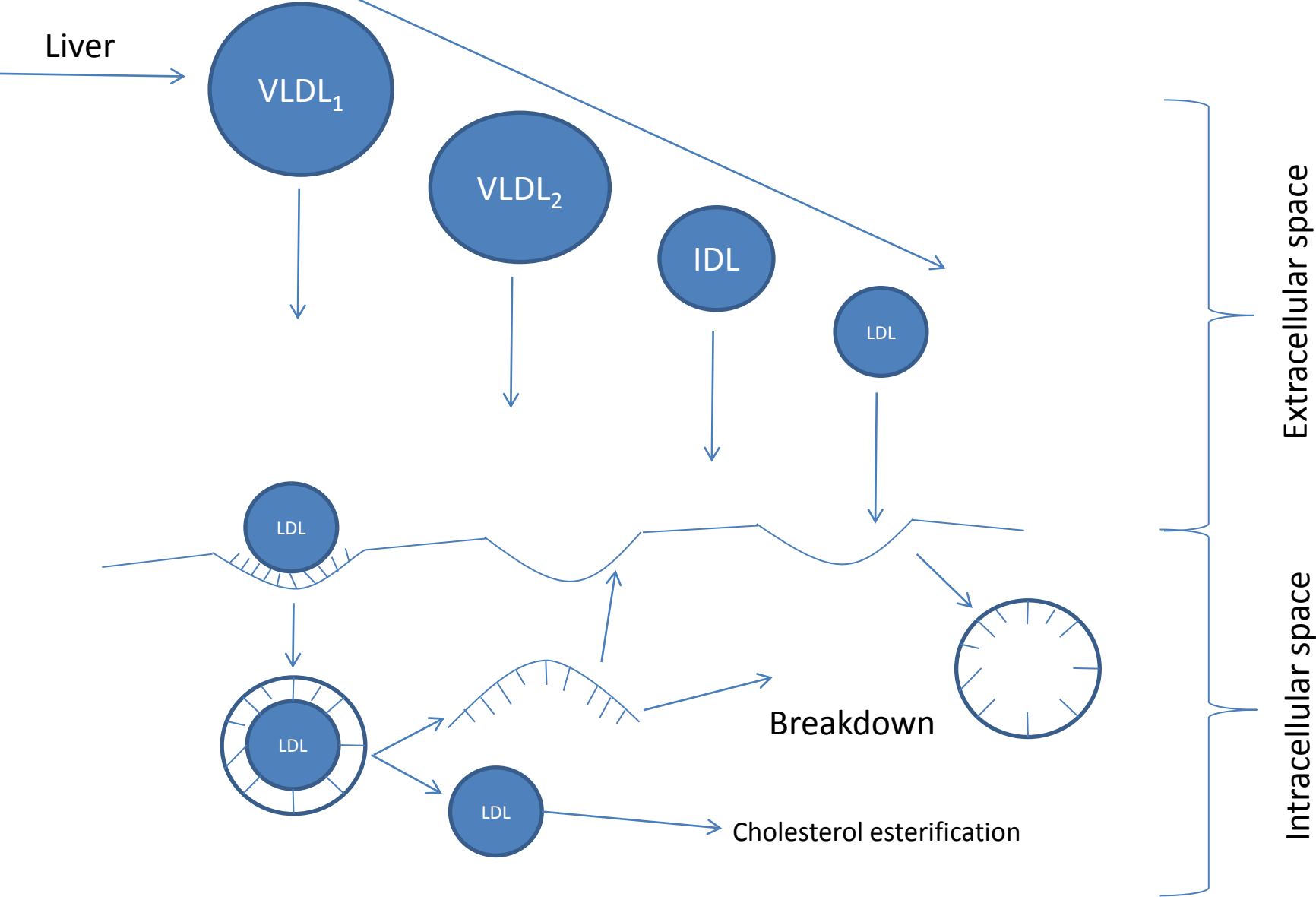
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# Lipoprotein Metabolism



# Models of Lipoprotein Metabolism

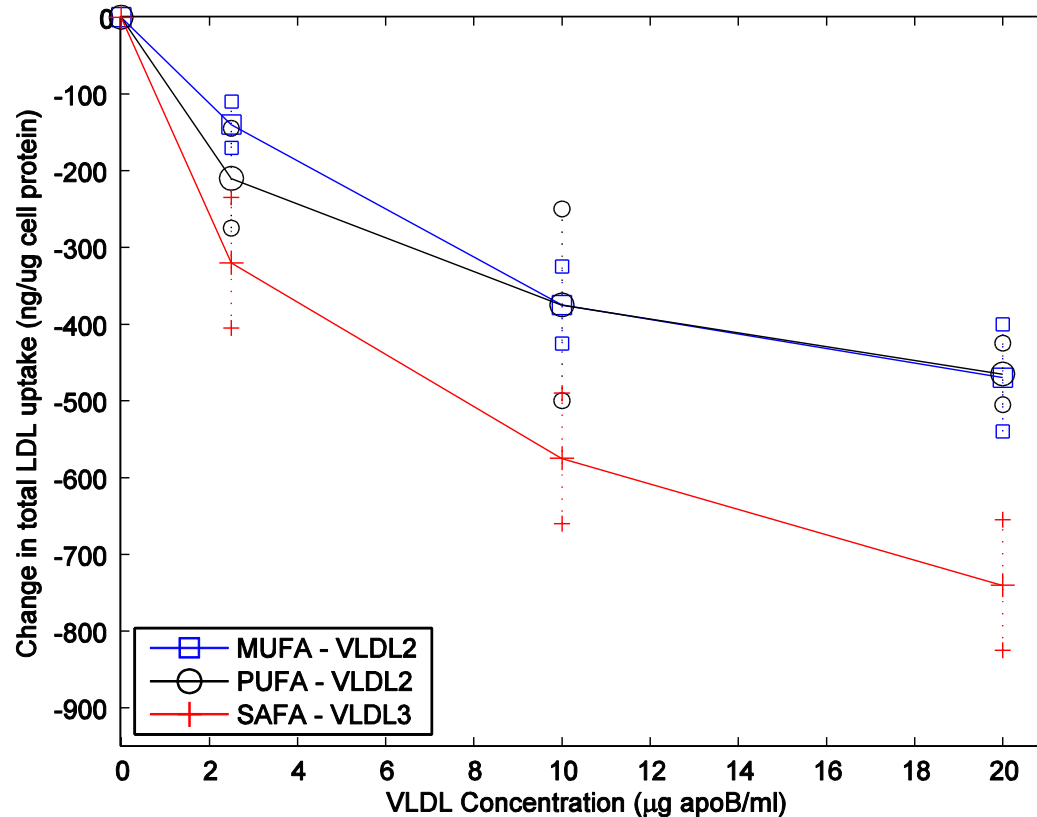
- **Receptor mediated endocytosis.**
  - **Looked at the competition between LDL and VLDL particles for receptors and its affect on intracellular cholesterol concentration.**
- **Genetic regulation of receptor and cholesterol biosynthesis .**
  - **Generated a new model of genetic regulation which gives interesting insight into homeostasis and disease states.**
- Developed a new model of VLDL to LDL delipidation which allows for particle heterogeneity to be examined in more detail.
- Recently looked at how we could extend our *in vitro* endocytosis models to the *in vivo* context.

# Models of Lipoprotein Metabolism

To develop well informed mathematical models, based upon current experimental understanding, which can be used to provide new insight into the mechanisms and process of lipoprotein metabolism and ultimately a predictive suite of models for testing current and providing new therapeutic strategies.

# Lipoprotein Endocytosis

- Consider the uptake of LDL and VLDL particles by a single hepatocyte cell.



Jackson, K., Maitin, V., Leake, D., Yaqoob, P. and Williams, C. (2006). Saturated fat induced changes in  $S_f$  60-400 particle composition reduces uptake of LDL by HepG2. *J. Lipid Res.*, 47:393-403.

# Hypothesis Testing

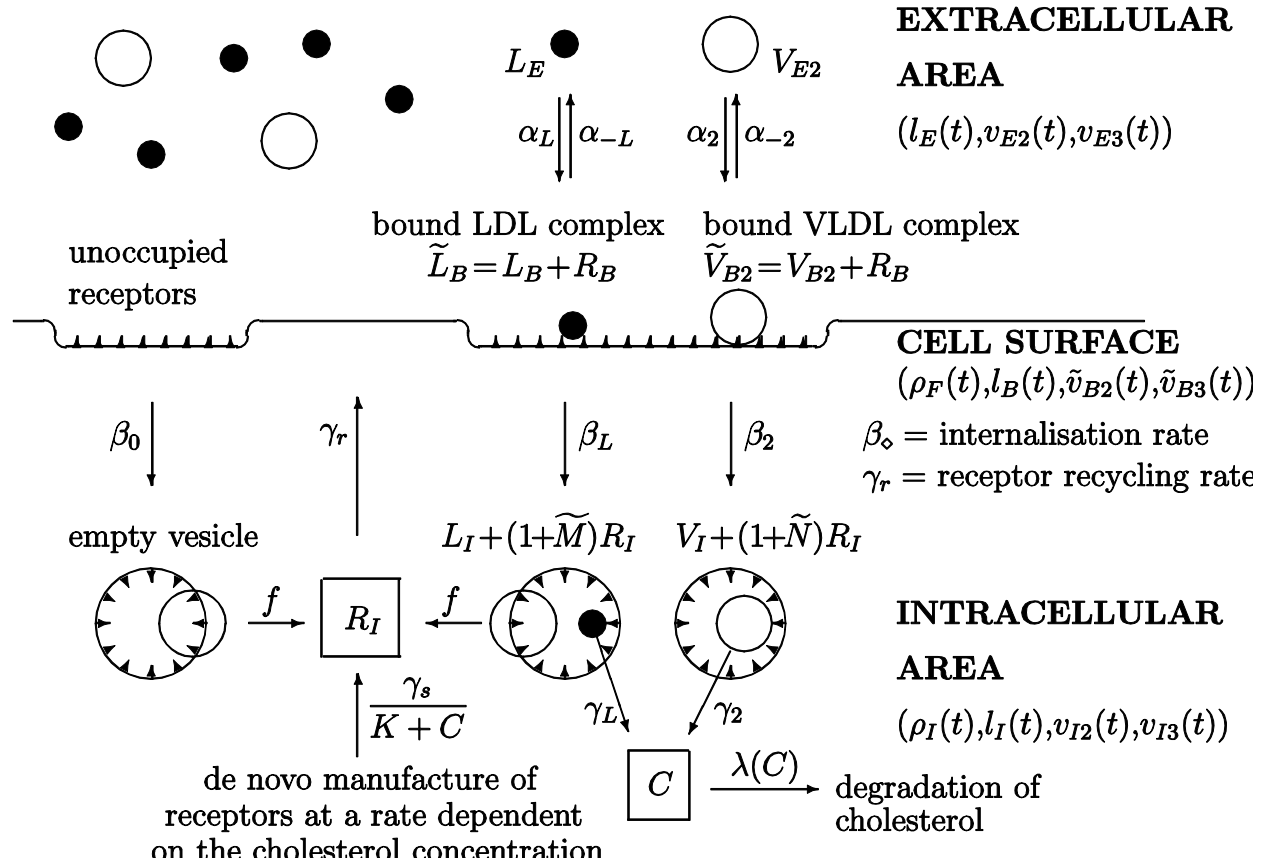
- Two hypothesis regarding LDL uptake

Hypothesis 1 – VLDL particles reduce LDL uptake by blocking access to hepatocyte surface receptors. Particles either bind to the surface and are not internalised or are simply present in the pit.

Hypothesis 2 – VLDL particles enter the pit, bind to receptors via apoE and are internalised by the cell.

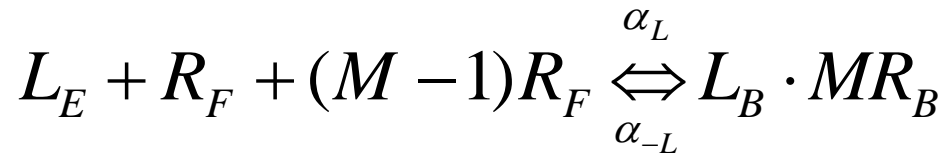
Which of these is correct?

# The Model

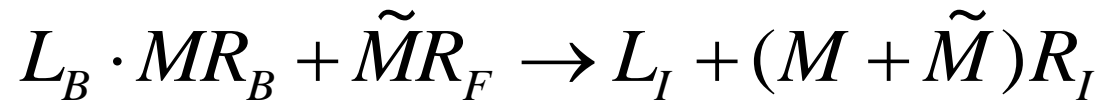


- LDL (extracellular, bound and intracellular).
- VLDL-2 (extracellular, bound and intracellular).
- VLDL-3 (extracellular, bound and intracellular).
- Free, bound and internalised receptors.
- Cholesterol concentration.

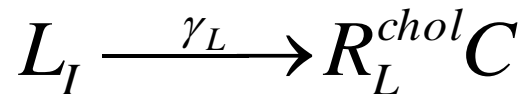
# The Model



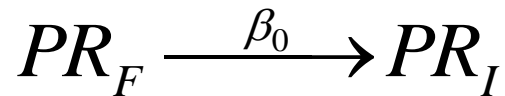
LDL binding



LDL and receptor  
internalisation



LDL to cholesterol  
release



Free receptor  
internalisation

# The Mathematical Model

$$W \frac{dl_E}{dt} = -\alpha_L \rho_F l_E + \alpha_{-L} l_B$$

$$\frac{dl_B}{dt} = \alpha_L \rho_F l_E - \alpha_{-L} l_B - \beta_L l_B$$

$$\frac{dl_I}{dt} = \beta_L l_B - \gamma_L l_I$$

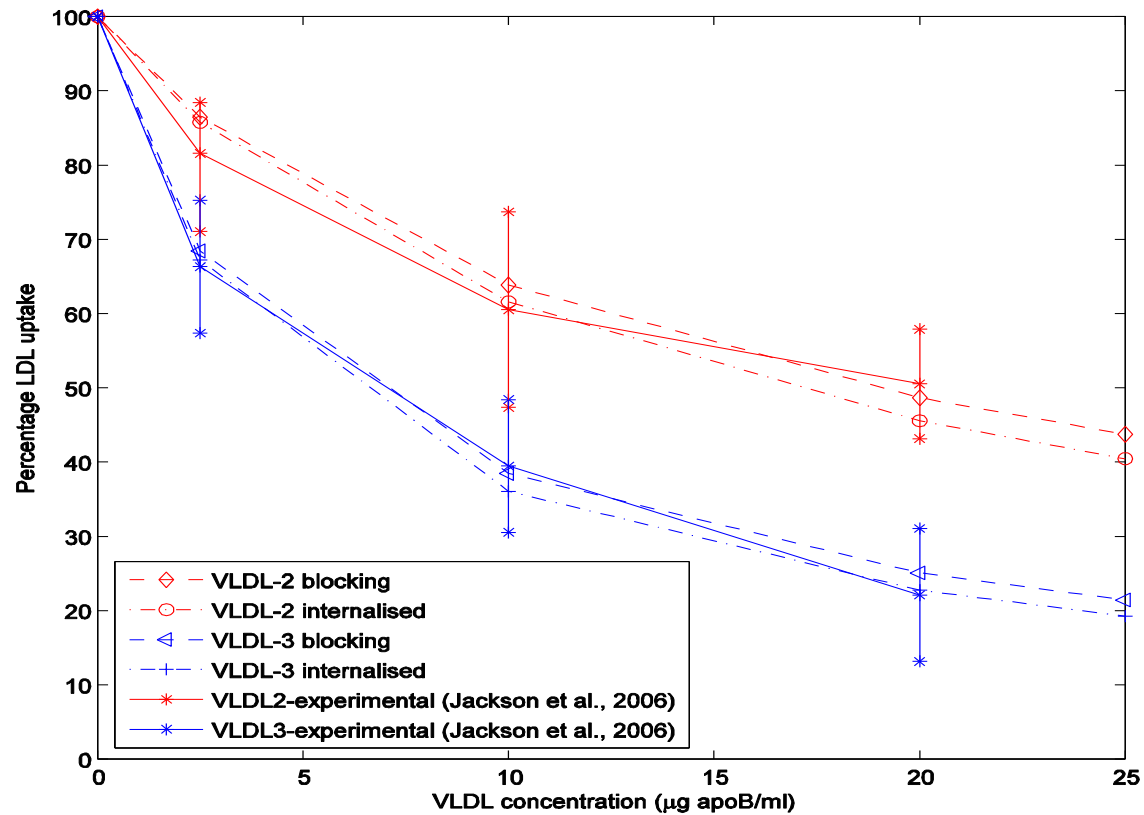
with

$$l_E(0) = l_0, \quad l_B(0) = 0, \quad l_I(0) = 0.$$

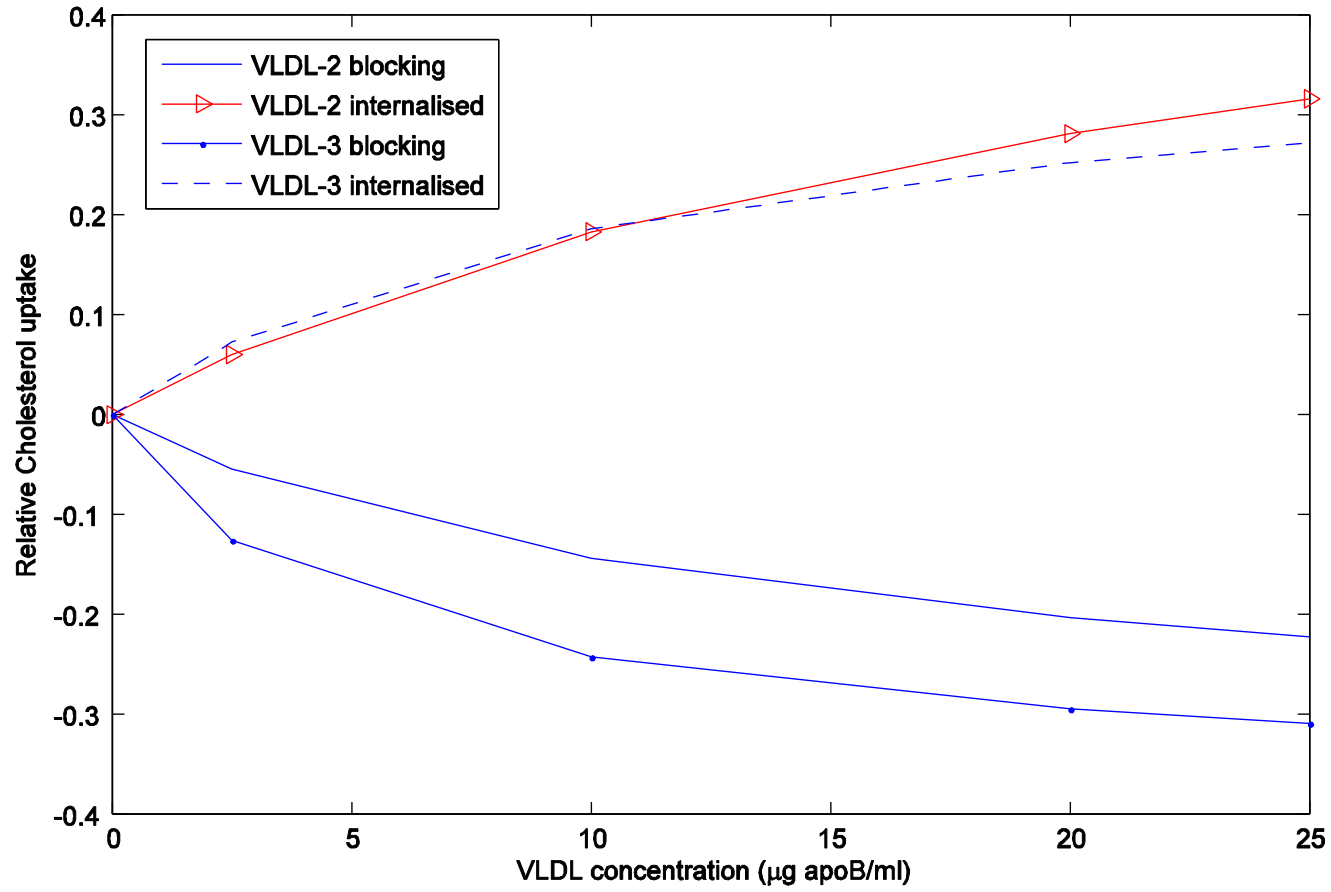
# Experimental Data

Parameter	Description	Value
$P$	Number of pits per cell.	180
	Number of receptors per cell.	35,000
	Number of receptors per pit (only 70% in pits).	180
	Radius of an LDL particle.	10nm
	Radius of a VLDL particle.	15-40 nm
	Typical radius of a pit.	100 nm
$M$	Number of receptors covered by a bound LDL.	1
$N$	Number of receptors covered by a bound VLDL-2.	2
$Q$	Number of receptors covered by a bound VLDL-3.	3.6
$\bar{M}, \bar{N}, \bar{Q}$	Maximum number of additional free receptors internalised.	$M, N, Q$
$\alpha_L$	Rate of LDL binding to free receptors.	$6.66 \times 10^{-17}$ ml/molecules s
$\alpha_2, \alpha_3$	Rate of VLDL-2, VLDL-3 binding to free receptors.	$14.0\alpha_L, 24\alpha_L$
$\beta_L$	Rate of LDL internalisation.	$2.7 \times 10^{-3} s^{-1}$
$\beta_2, \beta_3$	Rate of VLDL-2 and VLDL-3 internalisation.	$\beta_L$
$\beta_0$	Rate of unbound receptor internalisation.	0
$\alpha_{-L}$	Rate of LDL unbinding from receptors.	$5.9 \times 10^{-4} s^{-1}$
$\alpha_{-2}, \alpha_{-3}$	Rate of VLDL-2, VLDL-3 unbinding from receptors.	$0.5\alpha_{-L}, 0.33\alpha_{-L}$
$\gamma_L$	Rate of conversion of internalised LDL to cholesterol.	$\sim 1/300s$
$\gamma_2, \gamma_3$	Rate of receptor recycling from bound VLDL.	$\gamma_L$
$\gamma_r$	Rate of receptor recycling.	$0.01 s^{-1}$
$f$	Fraction of receptors recycled.	0.9
$K$	Constant for receptor production.	$2C_e$
$\gamma_i$	Rate of free receptor production by cell.	$1.8 \times 10^{20}$ molecules/mls
$\lambda$	Rate of breakdown of cholesterol.	$3.3 \times 10^{-3} s^{-1}$
$g_L^{chol}$	Average cholesterol content per LDL particle.	3400
$g_{V-2}^{chol}$	Average cholesterol content per VLDL-2 particle.	3100
$g_{V-3}^{chol}$	Average cholesterol content per VLDL-3 particle.	3900
$P_0$	Initial concentration of free receptors.	$2.5 \times 10^6$ /cell
$C_e$	Maximum cholesterol content of a hepatocyte.	$2.65 \times 10^{19}$ molecules/ml
$R_0$	Initial concentration of free receptors.	$2.17 \times 10^{10}$ receptors/ml
$h_0$	Initial concentration of LDL particles (mass/vol).	10 $\mu$ g/ml
$l_0$	Initial concentration of LDL particles (no./vol).	$1.17 \times 10^{13}$ particles/ml
$h_{02}/h_{00}$	Typical concentration of VLDL particles (mass/vol).	2.5, 10 and 20 $\mu$ g/ml
$h_{02}/h_{00}$	Initial concentration of VLDL particles (no./vol).	$2.95 \times 10^{12}, 1.17 \times 10^{13}$ and $2.35 \times 10^{13}$ particles/ml medium
$W$	Volume ratio of cell culture medium to cell volume.	$1.50 \times 10^3$
$h_2, h_3$	Hypothesis: if $h = 2$ , VLDL is internalised. if $h = 1$ , VLDL blocks and is not internalised.	12

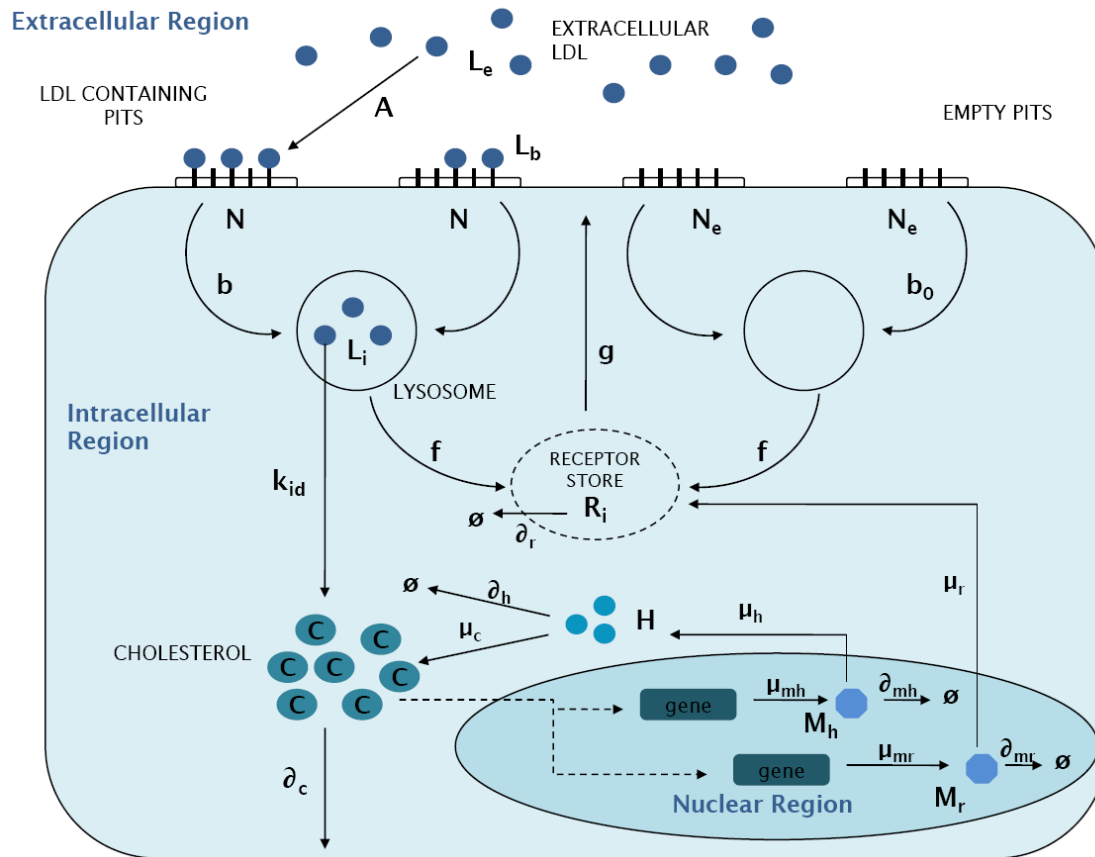
# Model and Experimental Comparisons



# New Insight



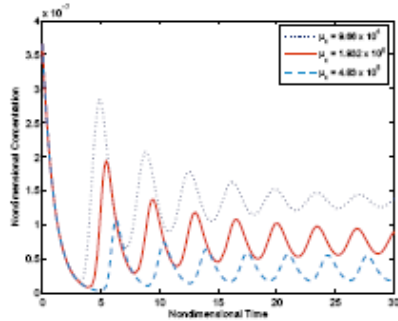
# Genetic regulation of receptor and cholesterol biosynthesis



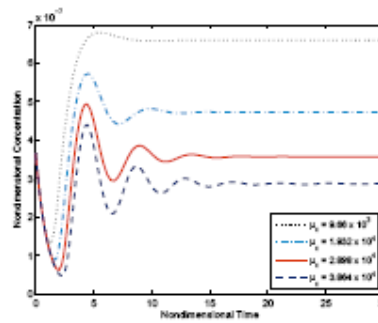
# Genetic regulation of cholesterol and receptor biosynthesis

- Model of genetic regulation which accounts explicitly for the number of binding sites available to the transcription factor on the DNA promoter region.
- Explicitly accounts for SREBP-SCAP pathway regulation by cholesterol, HMGR mRNA, HMGR protein, LDL mRNA and LDLR protein.
- Analysis of the HMGR system shows three distinct types of behaviour:
  - oscillatory homeostatic steady-state
  - damped oscillatory homeostatic steady-state;
  - non-oscillatory homeostatic steady-state.
- This is a result of the: (i) number of binding sites available to the DNA transcription factor (3) and number of molecules of cholesterol that can bind to a SREBP molecule (4); and range of parameter values considered.
- Comparison with experimental data indicates the oscillatory state may be possible.

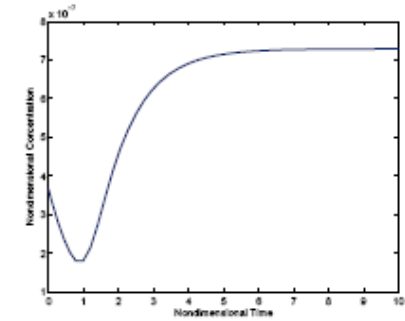
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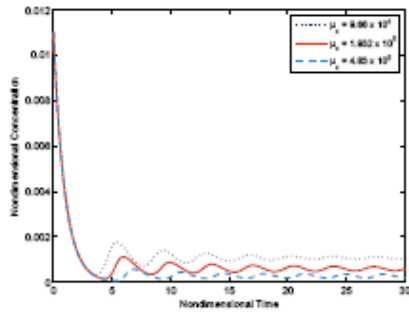
(a)



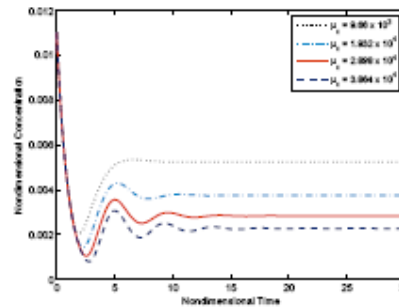
(a)



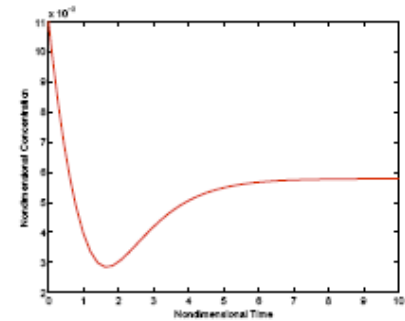
(a)



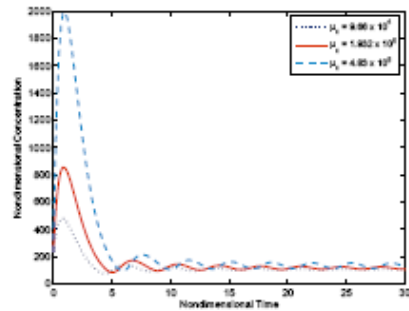
(b)



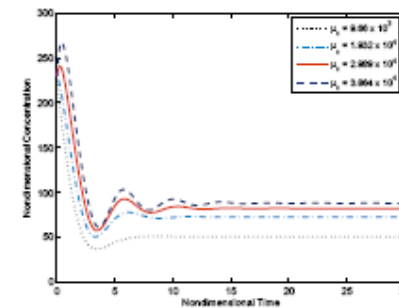
(b)



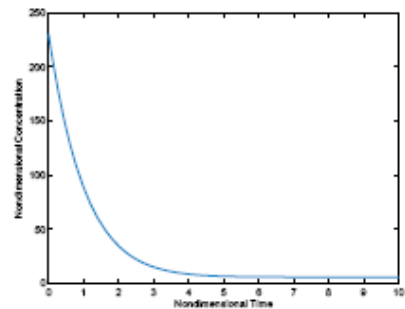
(b)



(c)



(c)



(c)

# Acknowledgements

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- Bonhi Bhattacharya, Department of Mathematics & Statistics, University of Reading.
- Dr Peter Sweby, Department of Mathematics & Statistics, University of Reading.
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# Publications

Wattis JA & Tindall MJ. An asymptotic comparison of mathematical models of lipoprotein endocytosis. Submitted to *Bull. Math. Biol.*

Tindall MJ, Wattis JA, O'Malley BJ, Pickersgill L, Jackson KG. A continuum receptor model of hepatic lipoprotein metabolism. *J. Theor. Biol.* 2009 Apr 7;257(3):371-84, 2009.

Pearson T, Wattis JA, O'Malley B, Pickersgill L, Blackburn H, Jackson KG & Byrne HM. Mathematical modelling of competitive LDL/VLDL binding and uptake by hepatocytes. *J. Math. Biol.* 2009 Jun;58(6):845-80.

Wattis JA, O'Malley B, Blackburn H, Pickersgill L, Panovska J, Byrne HM & Jackson KG. Mathematical model for low density lipoprotein (LDL) endocytosis by hepatocytes. *Bull. Math. Biol.* 2008 Nov;70(8):2303-33.