



Mathematical modelling of the role of HIF-1 in tumour growth

Alexander G. Fletcher, S. Jonathan Chapman, Christopher J.W. Breward

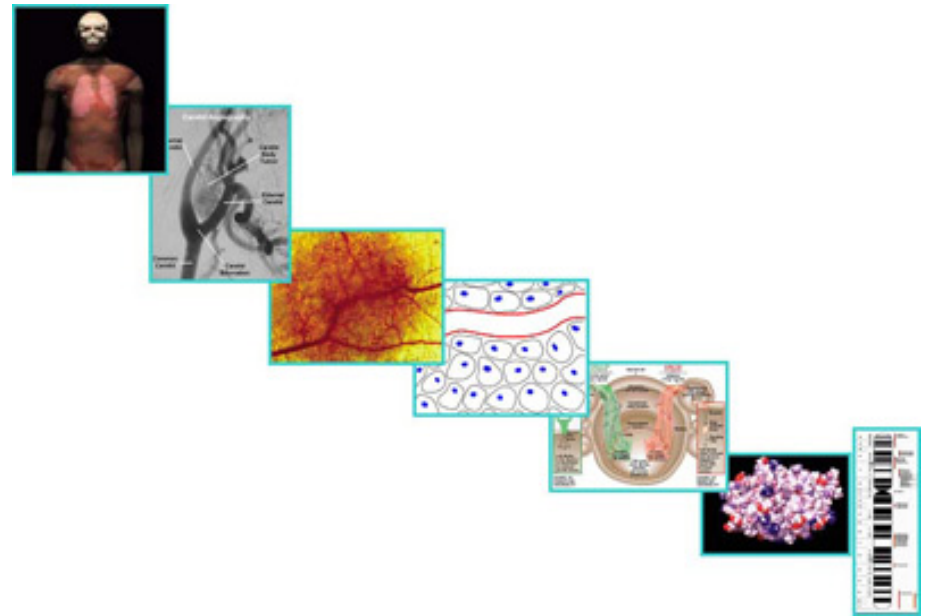
Mathematical Institute, University of Oxford

Outline of presentation

- Introduction
- Subcellular model
- Results
- Further work

The Integrative Biology Project

- The IB project aims to develop computational tools to simulate the heart and colorectal cancer
- The aim is to improve understanding of these two complex systems and test new therapies *in silico*
- This requires the understanding and multi-scale modelling of biological processes
- In order to understand how genetic mutations within a cell bestow it with cancerous properties, we need to model the complex genetic networks regulating cell physiology



<http://www.integrativebiology.ox.ac.uk/>

HIF-1 and the response to hypoxia

- The ability to sense and react to changes in oxygen concentration is an important aspect of cell physiology
- A cell responds to hypoxia through the hypoxia inducible transcription factor-1 (HIF-1)
- HIF-1 is a heterodimer consisting of HIF-1 α and HIF-1 β subunits
- Under hypoxic conditions, HIF-1 α interacts with HIF-1 β to form a transcriptionally active complex

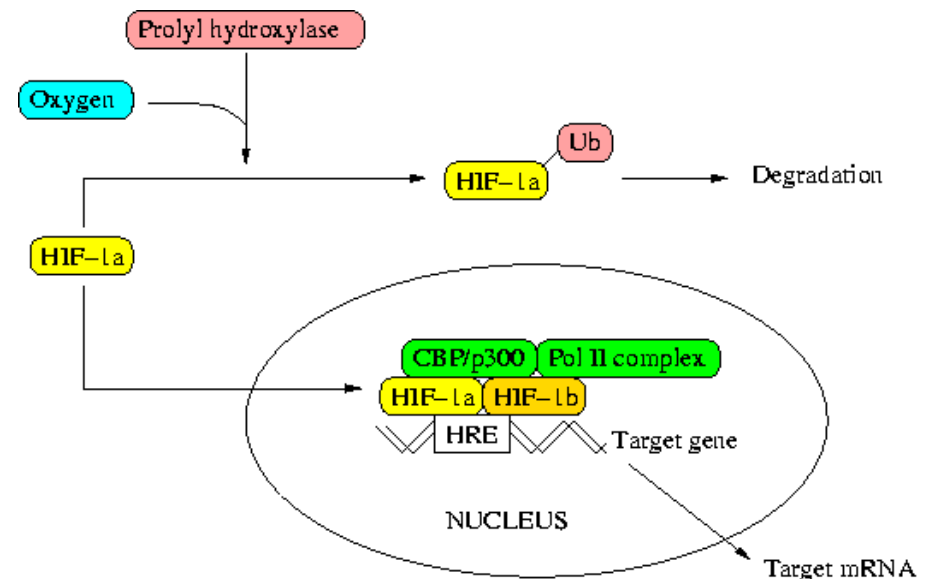
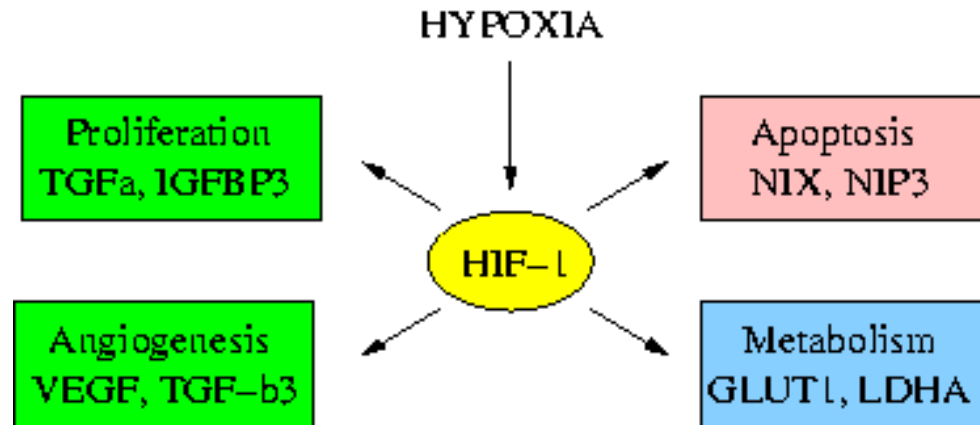


Diagram adapted from Harris, A.L. *Nat. Rev. Cancer* **2**, 38-47 (2002)

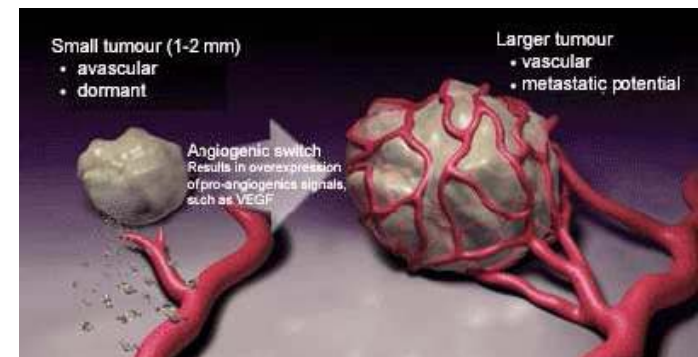
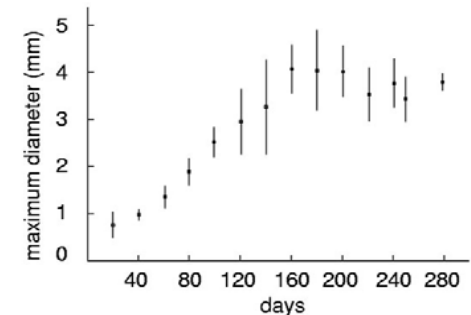
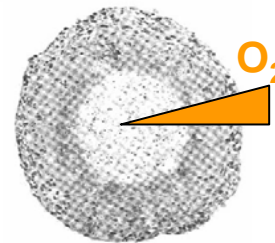
HIF-1 and the response to hypoxia (II)

- At least 70 putative HIF-1 target genes have so far been identified, and 5-10% of all human genes may be expressed in response to hypoxia in this way



Hypoxia and tumour growth

- Most solid tumours become hypoxic due to uncontrolled proliferation and the development of aberrant and leaky blood vessels
- Although hypoxia is toxic to both cancer cells and normal cells, cancer cells undergo genetic and adaptive changes that allow them to survive and even proliferate in a hypoxic environment
- Adaptation to hypoxic conditions is therefore a crucial step in tumour progression



Top diagram adapted from Folkman, J. and Hochberg, M. J. *Exp. Med.* **138**, 745-753 (1973)

Hypoxia and tumour growth (II)

- Under hypoxic conditions, a cell's fate is a result of competition between pro- and anti-apoptotic pathways and feedback from downstream pathways on HIF-1 production
- Although many tumour cells may be severely hypoxic, they have accumulated mutations that allow them to escape apoptosis
- Inhibition of HIF-1 activity has been proposed as a target for therapies
- To try to understand the complex role of HIF-1 in the adaptive response to hypoxia, we are investigating the specific interactions between HIF-1 and biomolecules involved in apoptotic signalling

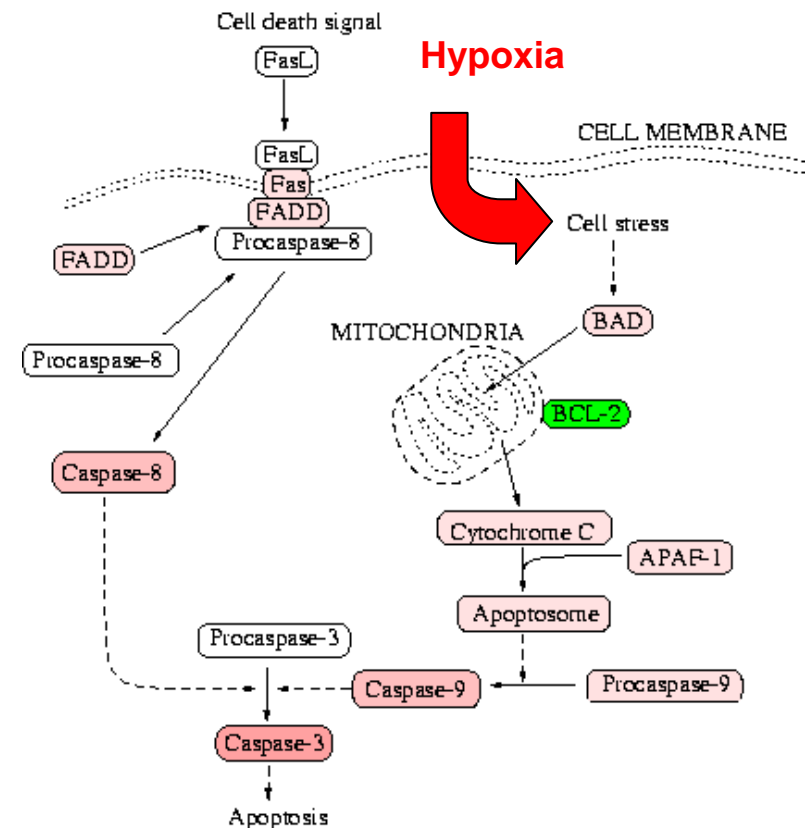
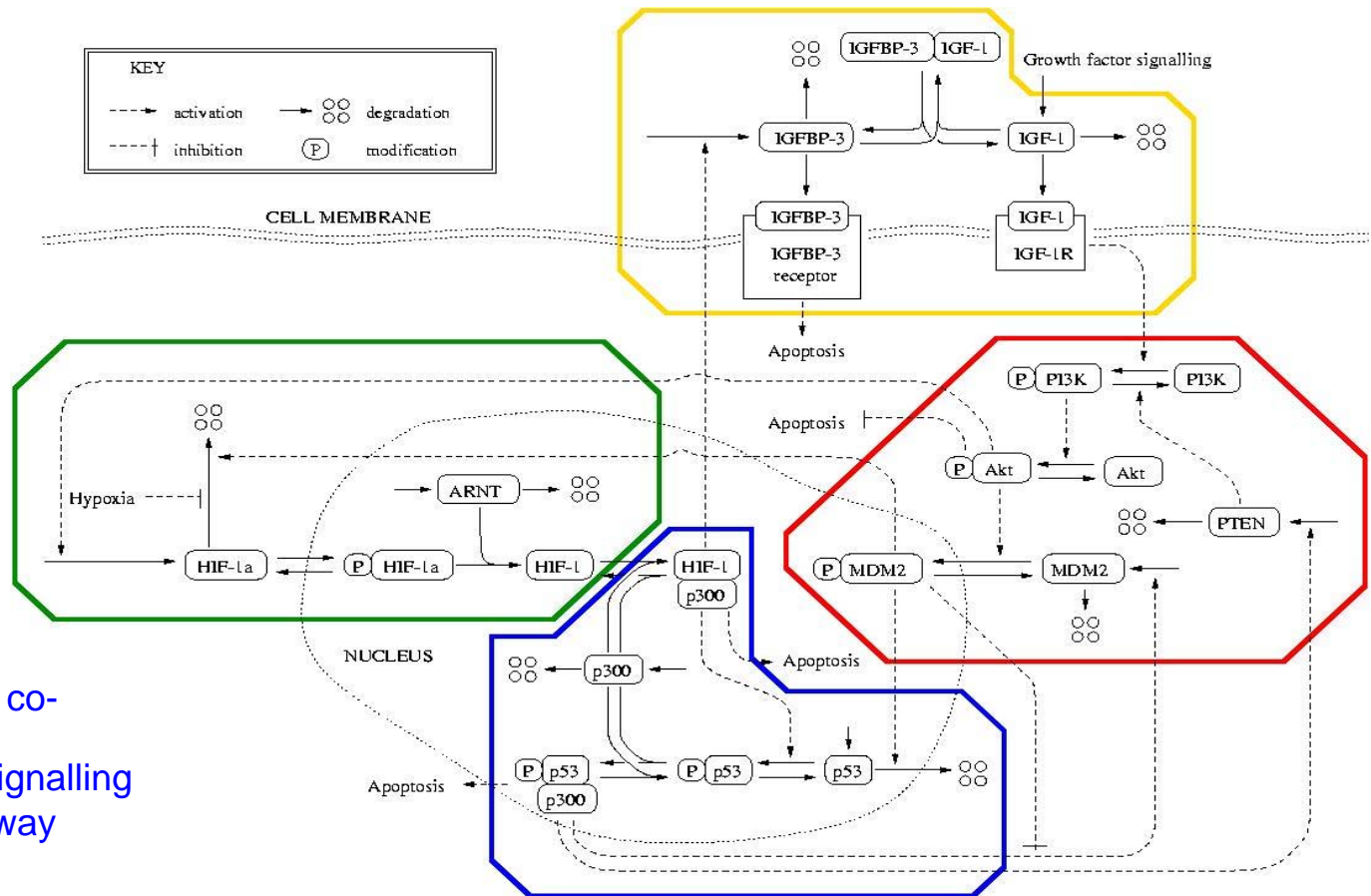


Diagram adapted from Semenza, G.L. *Physiol.* **19**, 176-182 (2004)

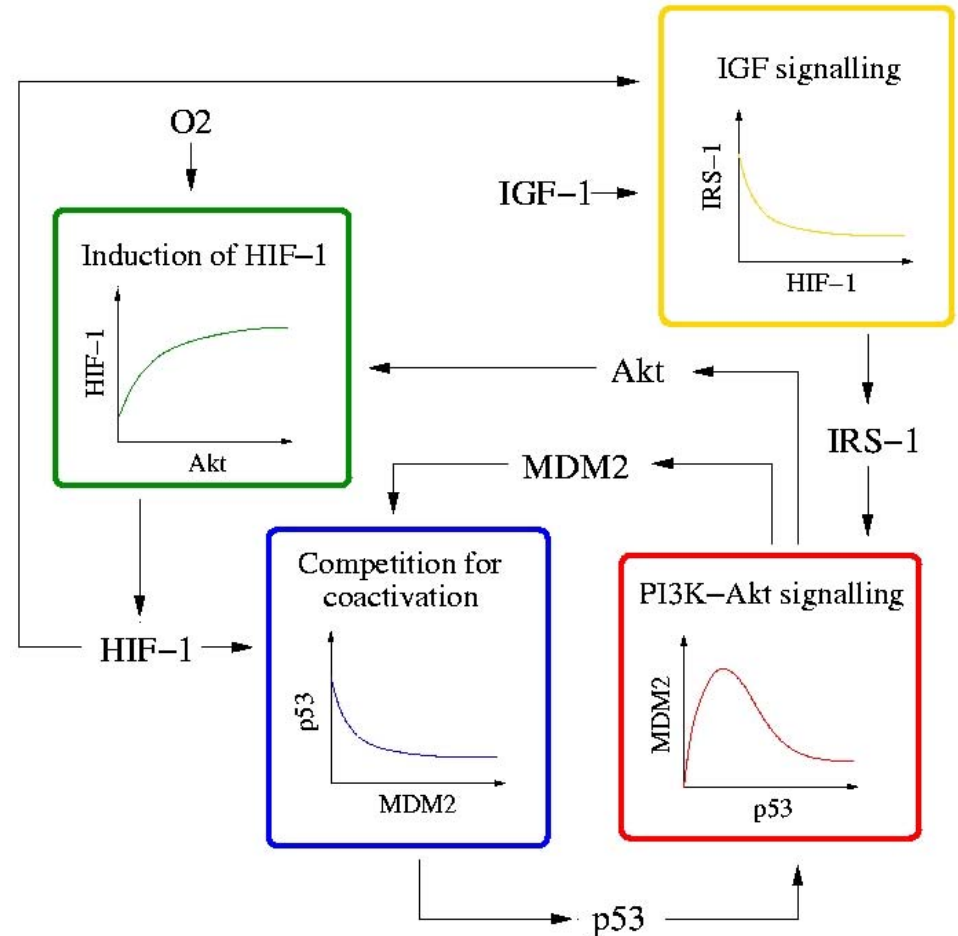
Subcellular model



- **Modules**
 - Competition for co-activators
 - Growth factor signalling
 - PI3K/AKT pathway
 - HIF-1 induction
- **Neglected downstream processes**

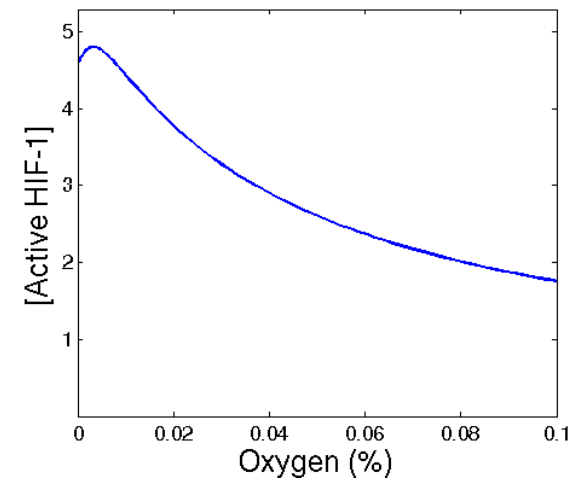
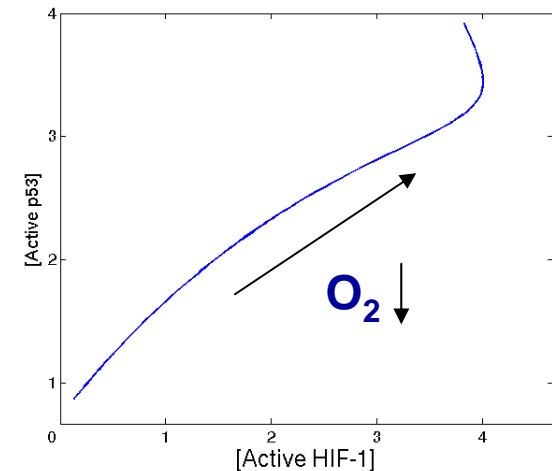
Subcellular model (II)

- Solve ODEs for the concentration of each species
- Obtain signal response curves for each module
- Parameter estimation
- Several feedback mechanisms in the model
- For example, IGF-1 growth factor signalling upregulates the synthesis of HIF-1a mRNA, while HIF-1 activates transcription of IGFBP-3, which sequesters IGF-1 away from cell surface receptors



Preliminary results

- We have hypothesized competition between HIF-1 and p53 for available co-activators¹
- This gives rise to a switching mechanism, in which significant upregulation of p53 activity occurs at much lower oxygen levels than that of HIF-1, which in turn leads to a slight decrease in HIF-1 activity, as observed experimentally²

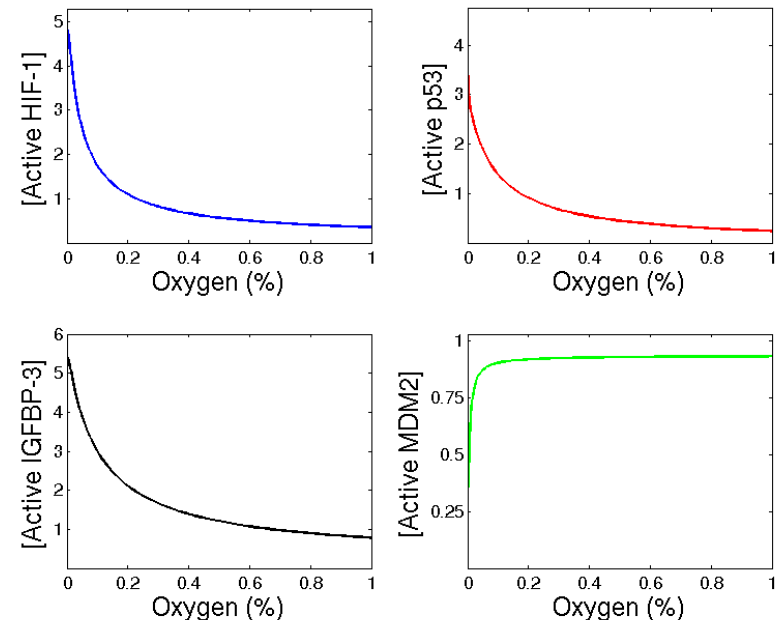


1. Schmid T. et al. *Biochem. J.* **380**, 289-295 (2004)

2. Jiang B-H. et al. *Am. J. Physiol. – Cell Ph.* **271**, C1172-1180 (1996)

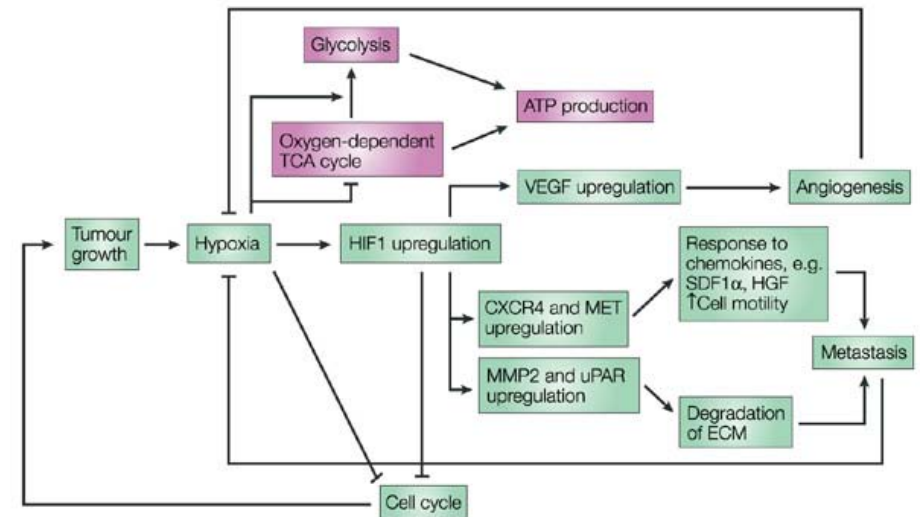
Preliminary results (II)

- The model predicts that in the absence of p53, we should observe the induction of more active HIF-1, and in p53 knockout cells, HIF-1 target genes should be transcribed sooner upon the onset of hypoxia
- The model also predicts that a chemotherapeutic drug (Avastin) that targets the downstream HIF-1 target VEGF will be more efficacious in p53 inactivated cells, since they will have more HIF-1 and thus synthesize more VEGF to target



Further work

- A great deal has been omitted from our current model; we intend to refine the model as more experimental data becomes available
- We will also extend our current model to include the dynamics of downstream effectors of apoptosis such as BAX and BNIP3 as well as anti-apoptotic factors such as BCL-2
- Other pathways affected by HIF-1, such as the glycolytic switch, may also be incorporated into the model

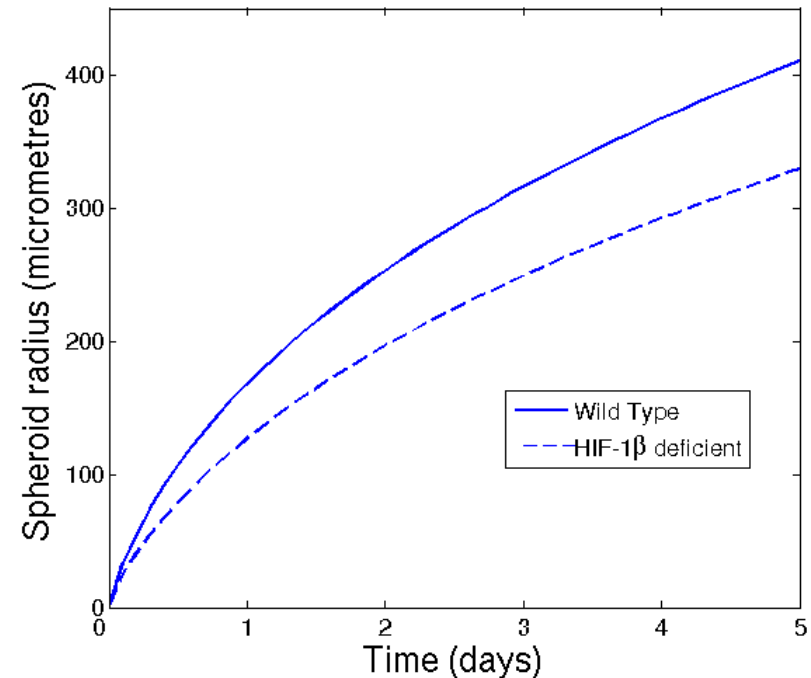


Nature Reviews | Cancer

Diagram adapted from Kitano, H. *Nat. Rev. Cancer* 4, 227-235 (2004)

Further work (II)

- To predict the response of a tumour at the tissue level, we developed a partial differential equation model of avascular tumour growth
- We considered the effect of inactivating HIF-1 β on the growth of a multicellular tumour spheroid, as has been investigated experimentally*
- Surprisingly, HIF-1 β inactivated cells grow slower than their wild type counterparts
- This example highlights the complex role of HIF-1 in the response to hypoxia
- In future work, we intend to model the interaction between wild type and mutant (e.g. HIF-1 inactivated) cell populations within a growing tumour



* Leek, R.D. et al. *Cancer Res.* **65**,4147-4152 (2005)

Acknowledgments

- Funded by EPSRC
- Jon Chapman and Chris Breward
- Philip Maini and others

- Adrian Harris
(Weatherall Institute of Molecular Medicine)



**Oxford Centre *for* Industrial
and Applied Mathematics**

