NCL-402 Review Presentation and JRF to SRF upgradation

Mathematical perspective in analyzing the skin as a complex biological system

Proposal: '*Multiscale model of human skin epidermis : response to ultraviolet radiation*'

Shraddha Puntambekar

2 July 2013

Chemical Engineering Division, National Chemical Laboratory

Outline of the presentation

- Human Skin
- Epidermis
- Melanocytes
- Constitutive pigmentation
- Facultative pigmentation
- Proposal
- Preliminary Work

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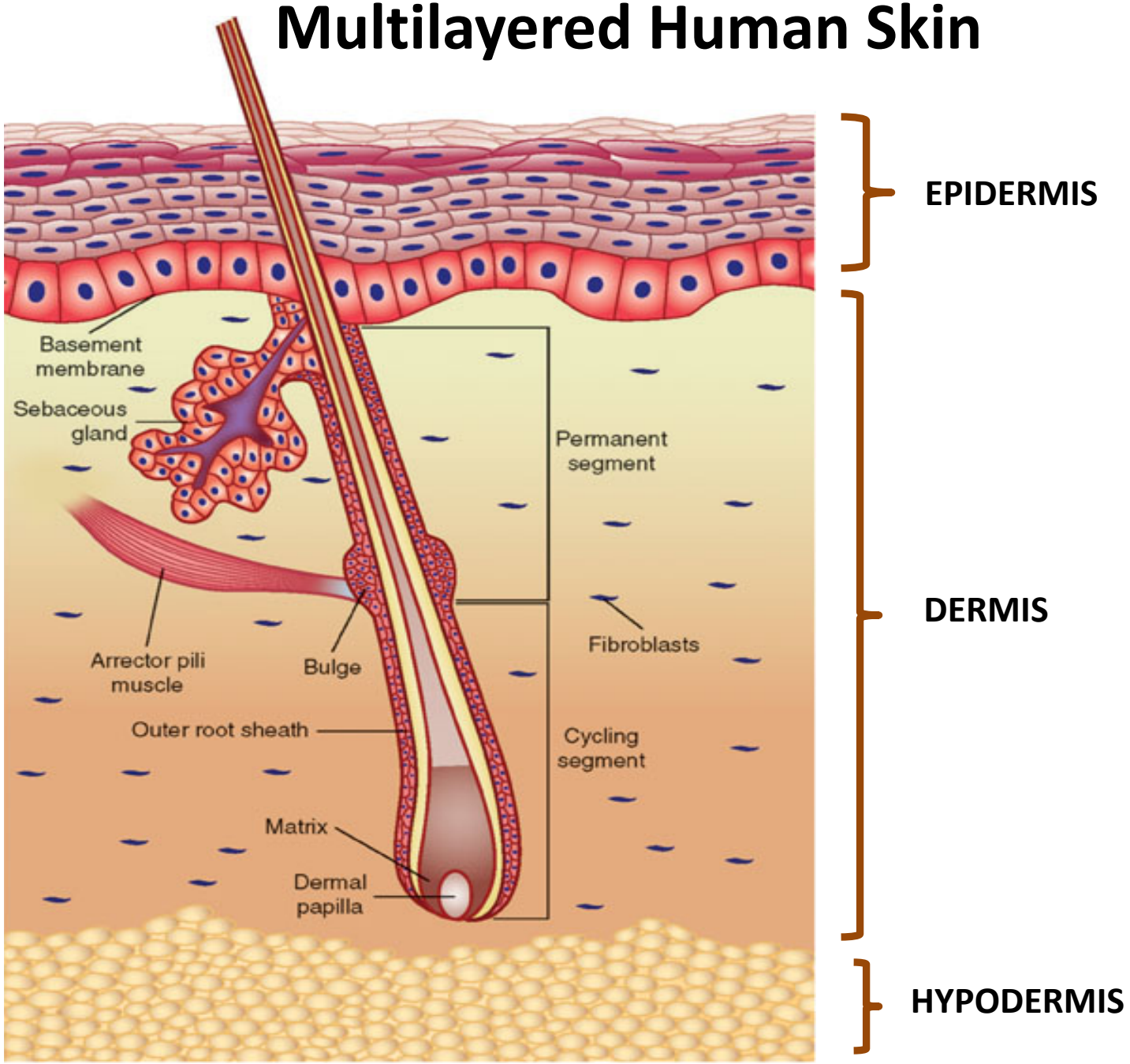
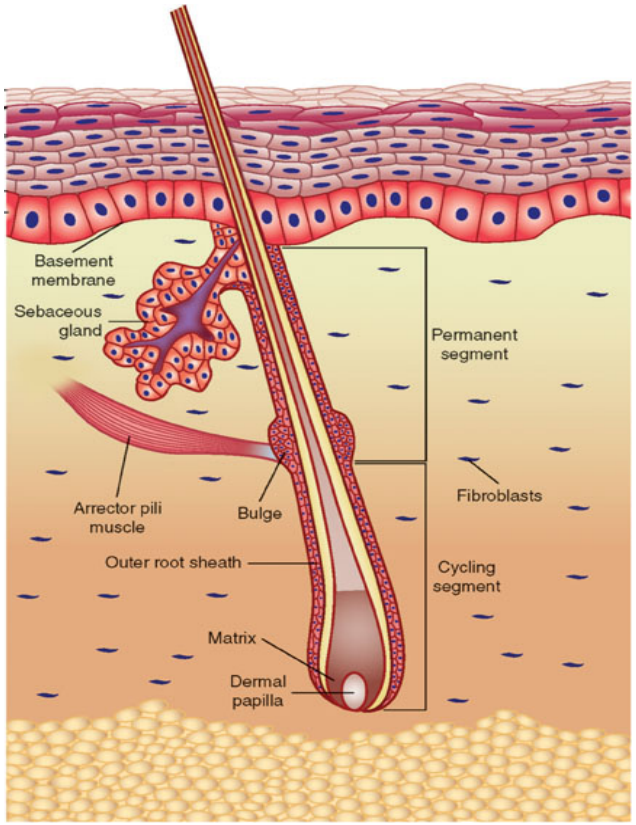
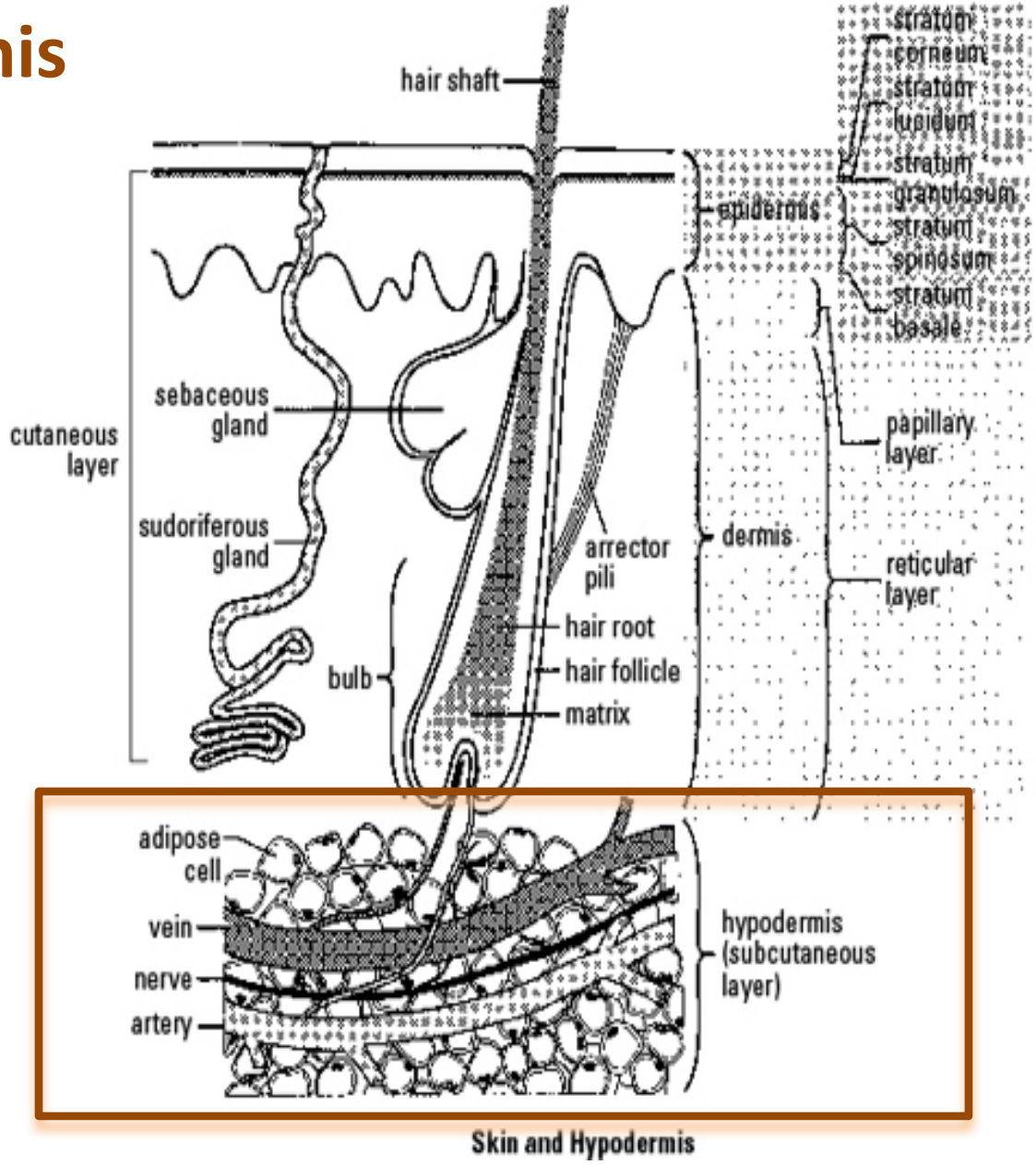
Multilayered Human Skin



Ref: Wong, D.J. and H.Y. Chang, *Skin tissue engineering. 2009.*

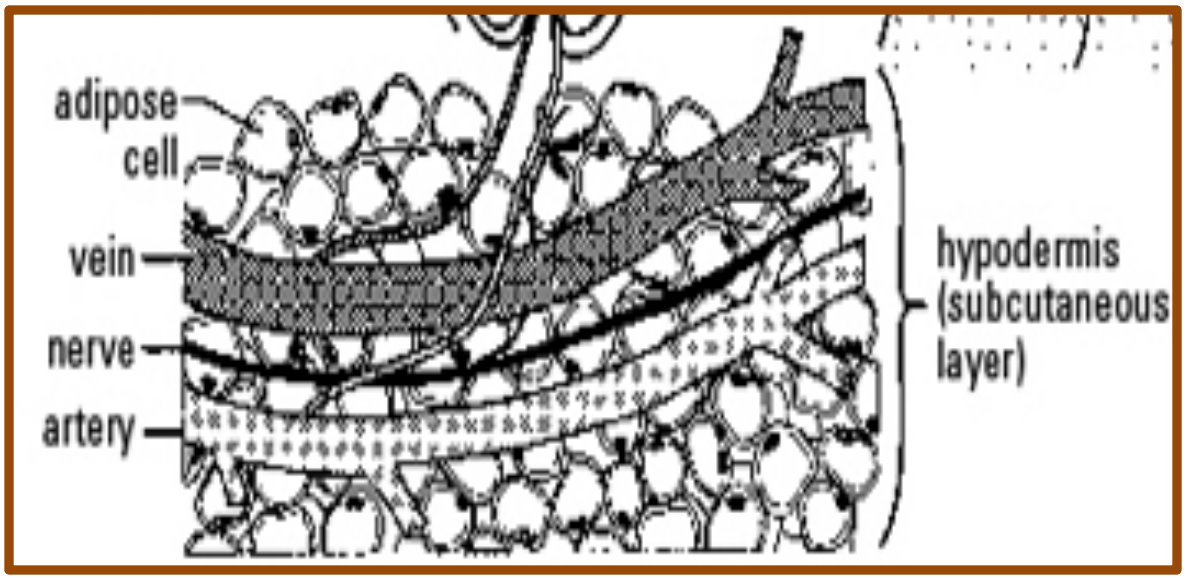
Hypodermis





Ref: http://www.cliffsnotes.com/sciences/anatomy-and-physiology/the-integumentary-system/the-skin-and-its-functions

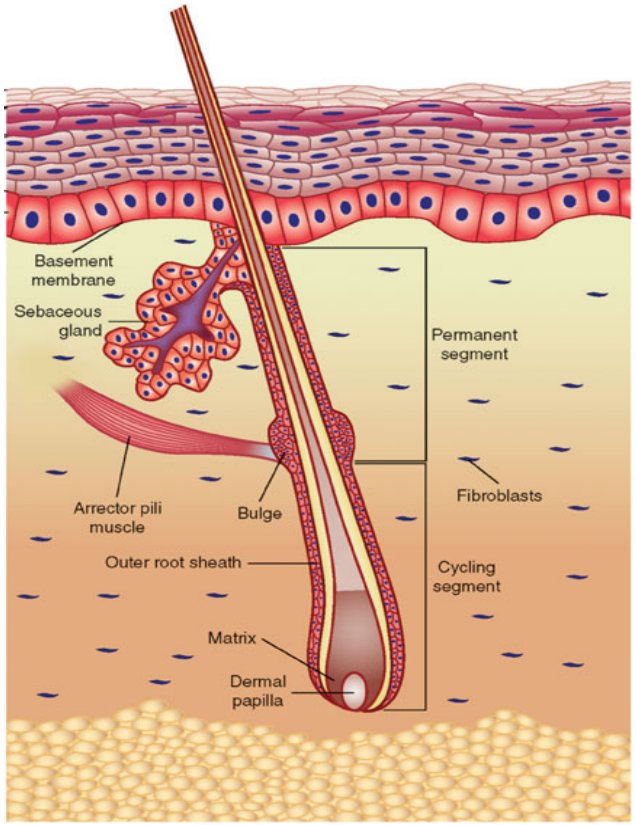
Hypodermis

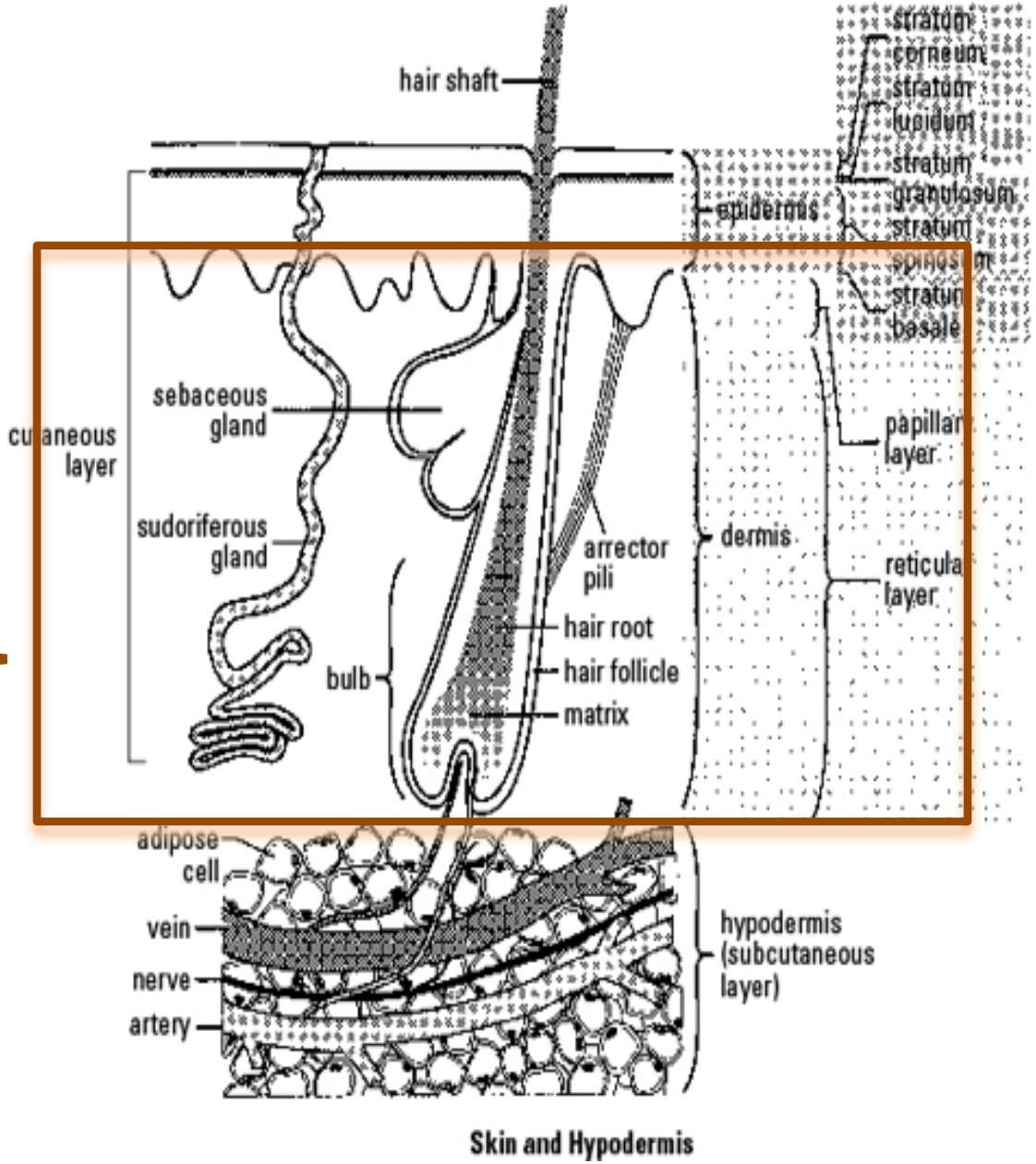


- Is composed of adipocytes which are separated by connective tissue
- It connects the skin layers with internal bones and organs
- It stores fat and is source of energy
- provides padding

Ref:http://www.cliffsnotes.com/sciences/anatomy-and-physiology/the-integumentary-system/the-skin-and-its-functions

Dermis

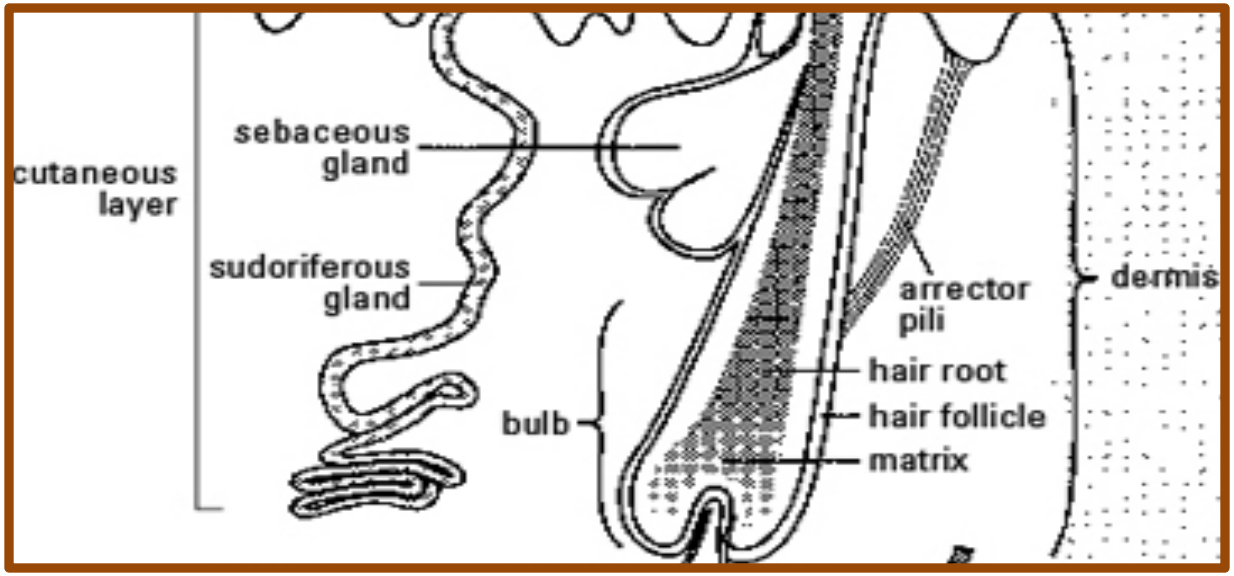




Skin and Hypodermis

Ref: http://www.cliffsnotes.com/sciences/anatomy-and-physiology/the-integumentary-system/the-skin-and-its-functions

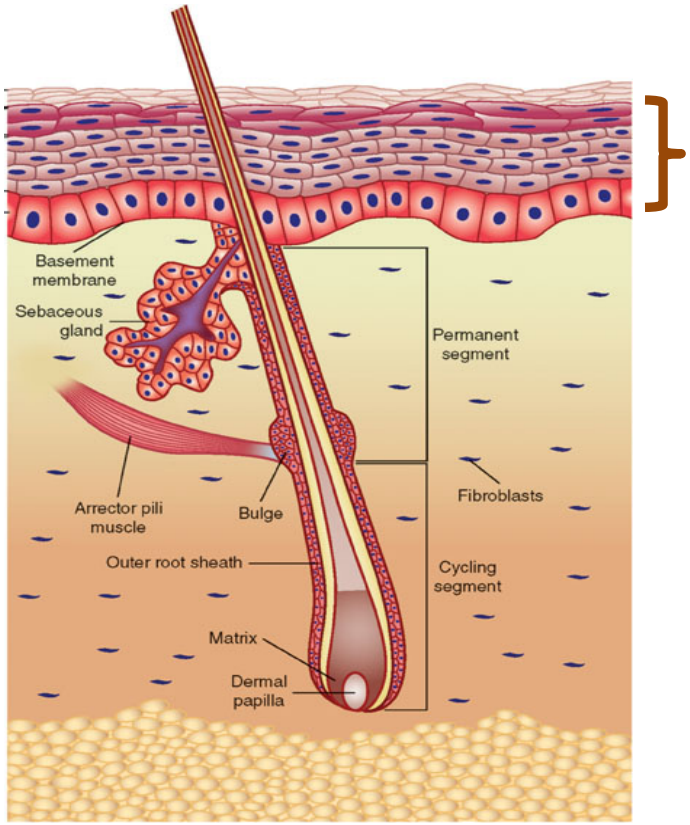
Dermis

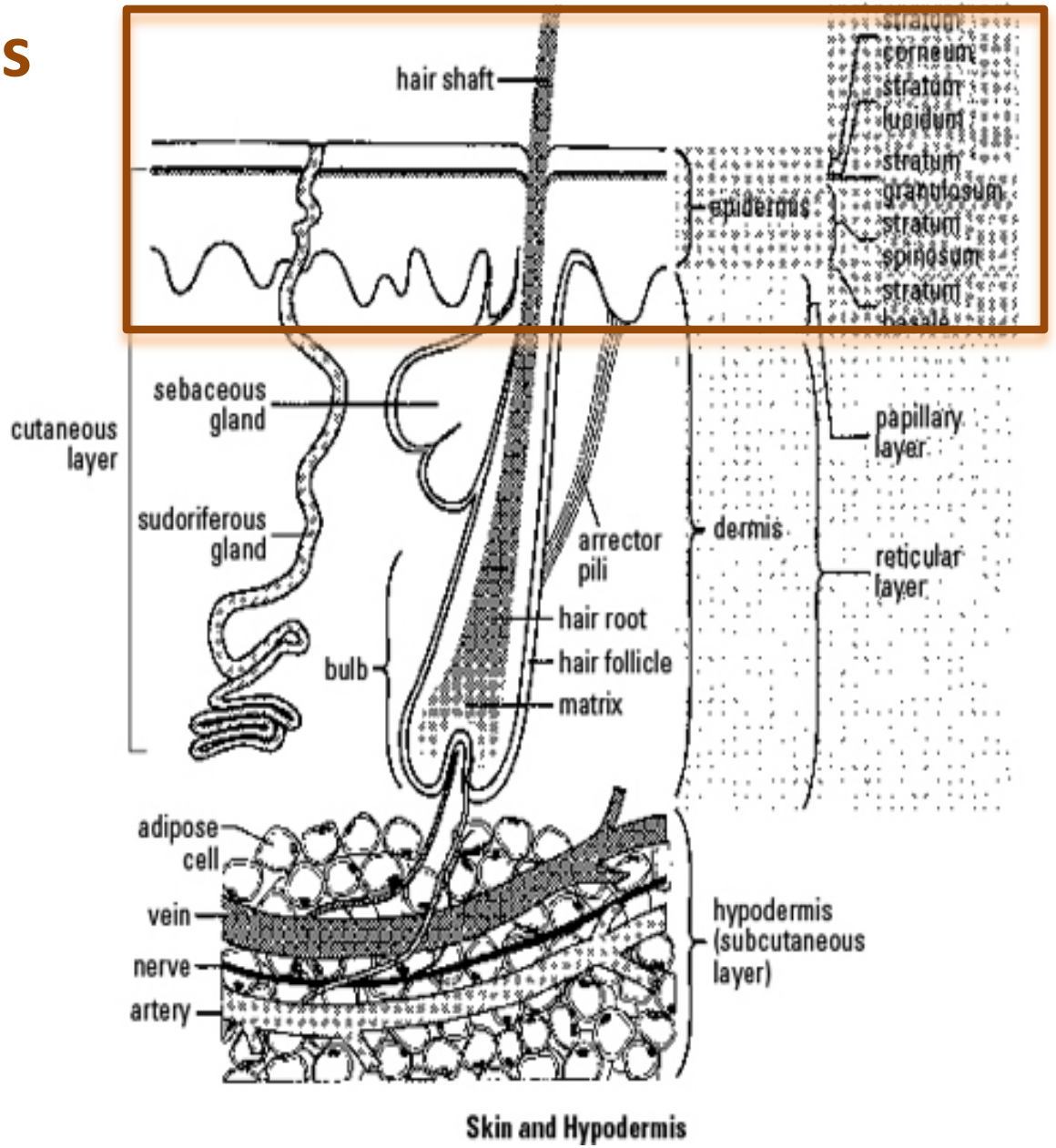


- Is divided into two layers, the superficial area adjacent to the epidermis called the papillary region and a deep thicker area known as the reticular dermis.
- The blood vessels in the dermis provide nourishment to the upper epidermal layer.
- Sebaceous gland, hair follicle is situated in the dermis

Ref:http://www.cliffsnotes.com/sciences/anatomy-and-physiology/the-integumentary-system/the-skin-and-its-functions

Epidermis

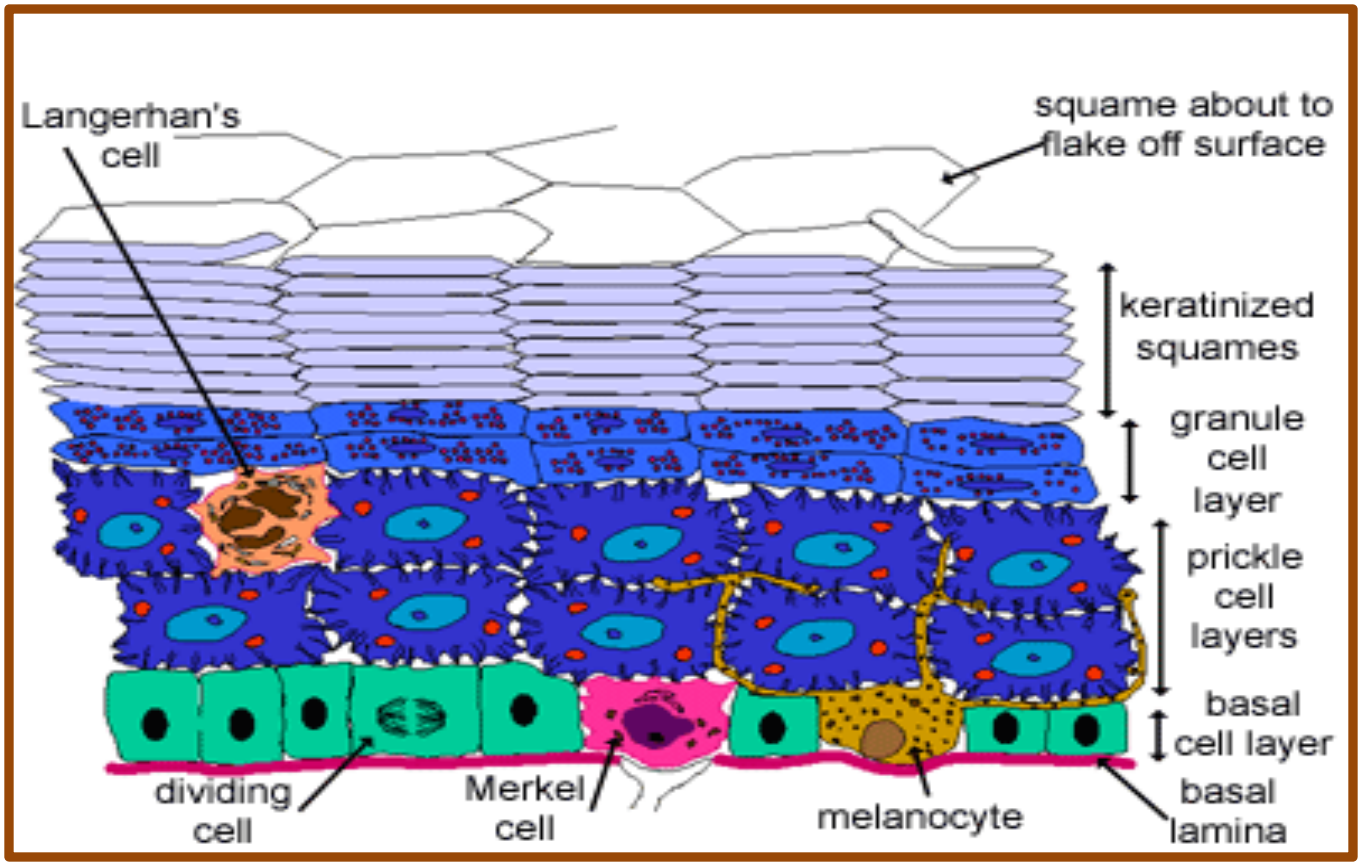




Skin and Hypodermis

Ref: http://www.cliffsnotes.com/sciences/anatomy-and-physiology/the-integumentary-system/the-skin-and-its-functions

Epidermis



- Keratinocytes form 95% of total epidermal cell content.

- Basement membrane plays an important role in keratinocyte differentiation

Ref: University of Leeds (2003) *The histology guide*

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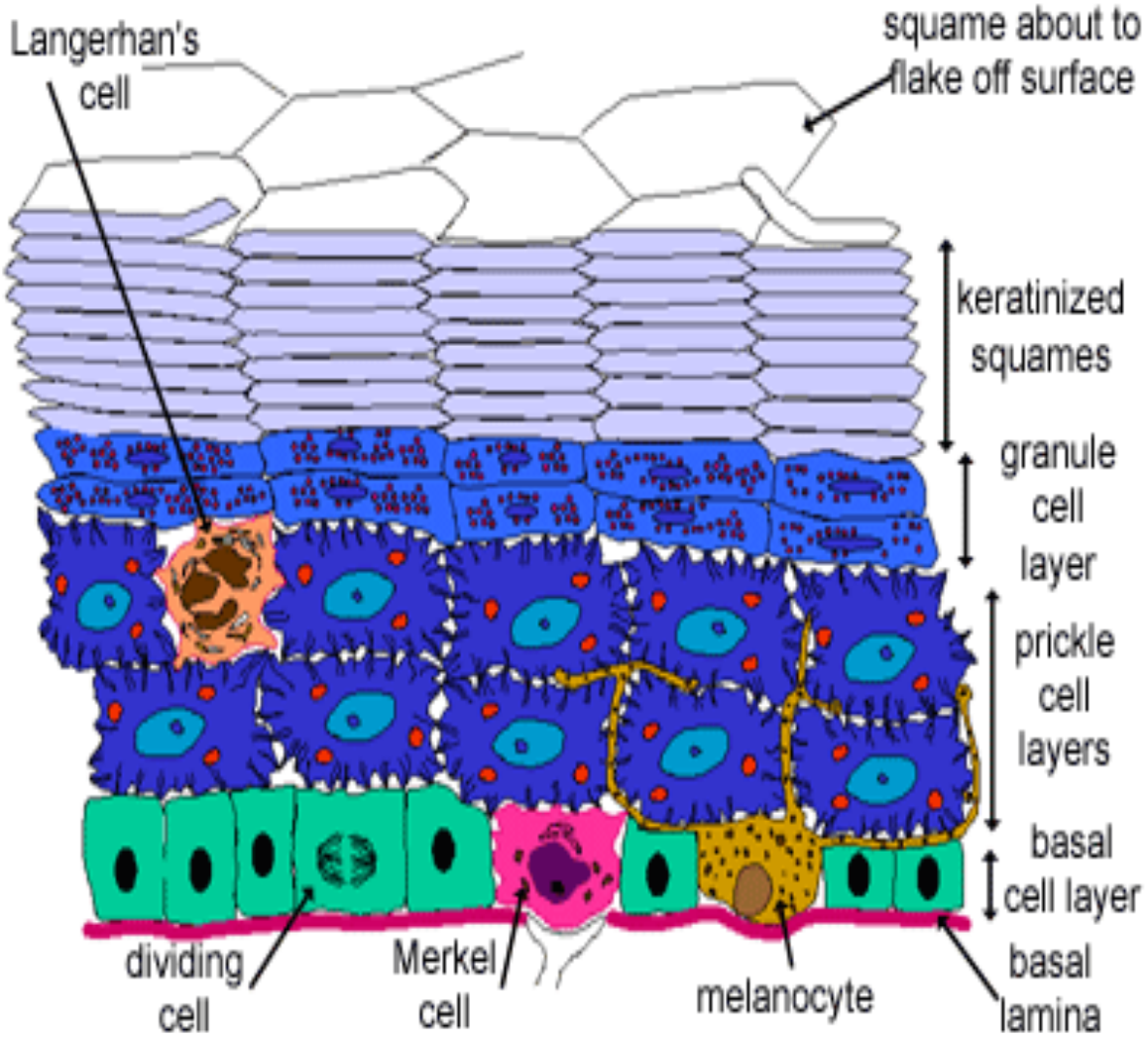
Four epidermal layers of differentiating keratinocytes



Stratum corneum (10-20 layers)

Stratum granulosum (3-5 layers)

Stratum spinosum (8-10 layers)

Stratum basal (single layer)

Keratinocyte differentiation

0163-769X/03/$20.00/0
Printed in U.S.A.

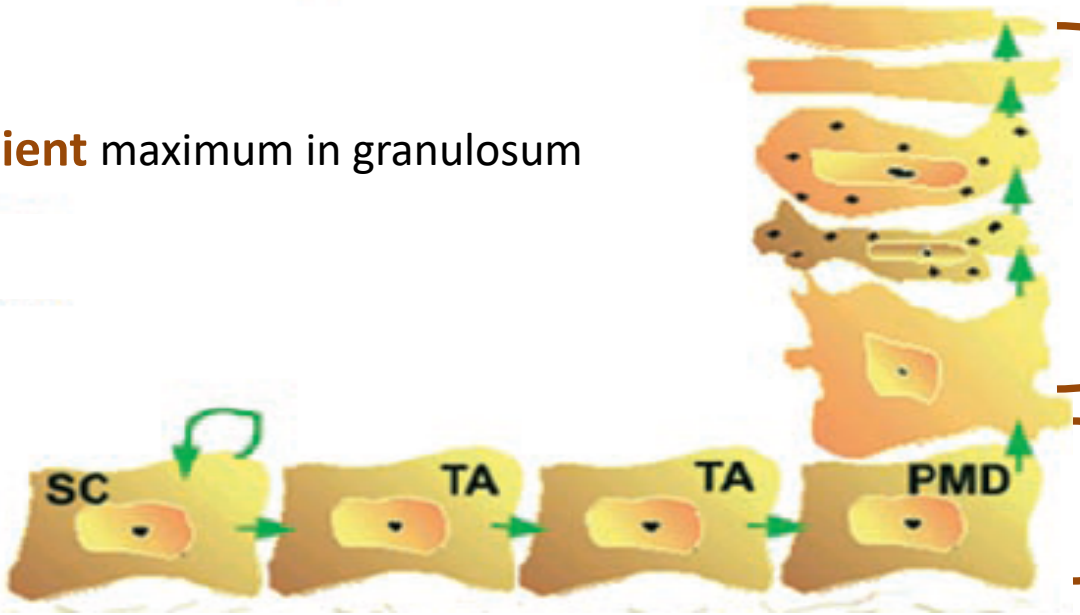
Endocrine Reviews 24(6):737–764

doi: 10.1210/er.2002-0021

Epidermal Homeostasis: The Role of the Growth Hormone and Insulin-Like Growth Factor Systems

STEPHANIE R. EDMONDSON, SUSAN P. THUMIGER, GEORGE A. WERTHER, AND CHRISTOPHER J. WRAIGHT

Calcium gradient maximum in granulosum



Differentiated suprabasal layer

Proliferating, self renewed Basal layer

- Keratinocyte differentiation in the epidermis is in part mediated by a calcium gradient.

Epidermal turnover

- Epidermal turnover - The whole epidermis is renewed every 2-4 weeks.

- Desquamation – Shedding of the corneocytes, the outermost layer of the skin
  - Non pathologic desquamation of the skin occurs after epidermal turnover
  - Pathologic desquamation seen in X linked icthyosis, after burn or shock – cells are shed in clusters hence forms visible scale

Photodermatol Photoimmunol Photomed 1997: 13: 153–158
Printed in Denmark · All rights reserved

Photodermatology
Photoimmunology
& Photomedicine
ISSN 0905-4383

Epidermal thickness, skin pigmentation and constitutive photosensitivity

Epidermal thickness – independent of skin type - But Intra variation observed at different body sites with buttocks having thickest epidermis

Stratum corneum – Thickness is positively correlated to pigmentation and negatively to smoking - independent of age and gender

Of viable layers – positively correlated to blood content and was observed to be thicker in males

Acta Derm Venereol 2003; 83: 410–413

Taylor&Francis
healthsciences

INVESTIGATIVE REPORT

Epidermal Thickness at Different Body Sites: Relationship to Age, Gender, Pigmentation, Blood Content, Skin Type and Smoking Habits

JANE SANDBY-MØLLER[1], THOMAS POULSEN[2] and HANS CHRISTIAN WULF[1]

[1] Department of Dermatology, Bispebjerg Hospital, University of Copenhagen, Copenhagen and [2] Department of Pathology, Sønderborg Sygehus, Sønderborg, Denmark

Mathematical Models

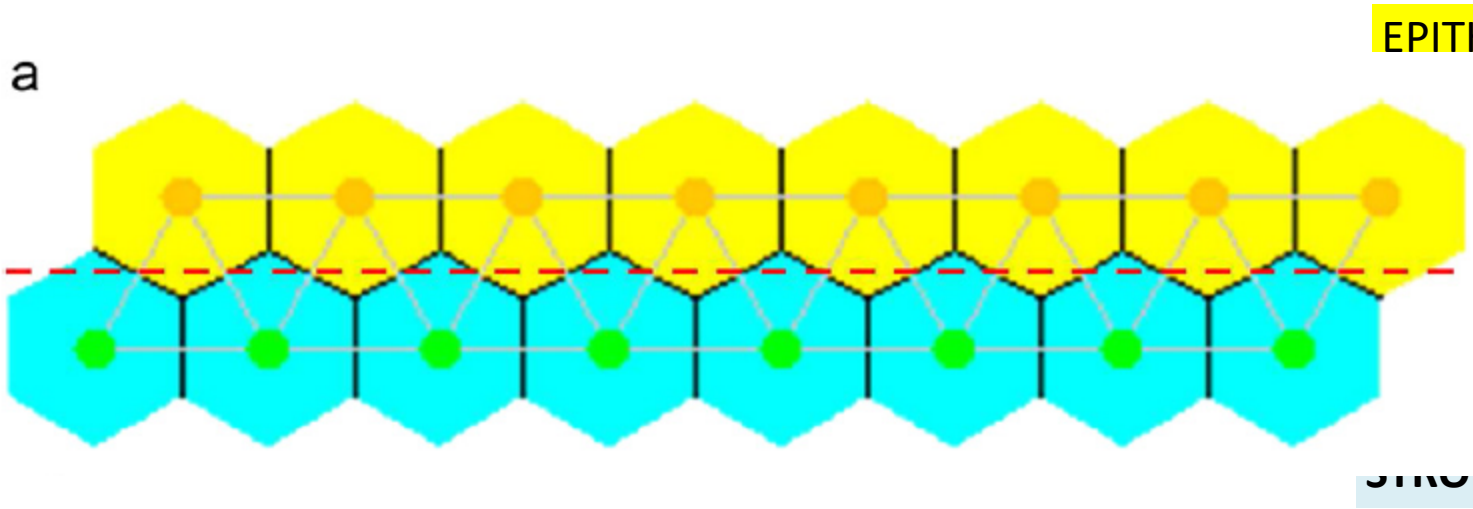
1. Of Basement membrane (BM)
2. Epithelial homeostasis in colonic crypt
3. Model of solute/drug transport in the epidermis
4. Models to study optical properties of the skin
5. Multiscale model of hair

1.

Modelling the role of the basement membrane beneath a growing epithelial monolayer

Sara-Jane Dunn [a,*], Alexander G. Fletcher [b,c], S. Jonathan Chapman [b], David J. Gavaghan [a,c], James M. Osborne [a,c]

[a] Department of Computer Science, University of Oxford, Wolfson Building, Parks Road, Oxford, OX1 3QD, UK
[b] Mathematical Institute, 24-29 St. Giles', Oxford, OX1 3LB, UK
[c] Oxford Centre for Integrative Systems Biology, Department of Biochemistry, South Parks Road, Oxford, OX1 3QU, UK



A discrete, off-lattice cell-centre model is constructed for the BM for the range of biological epithelia.

The model simulations show that the homeostasis of the growing epithelia can be achieved and sustained.

2.

Multiscale model for intestinal Crypt lined by continuously renewed epithelium

Cell migration and organization in the intestinal crypt using a lattice-free model

F. A. Meineke*, C. S. Potten† and M. Loeffler*

**Institute for Medical Informatics, Statistics and Epidemiology, Leipzig, Germany, and †Paterson Institute, Manchester, UK*

Received 16 *October* 2000; *revision accepted* 29 *March* 2001

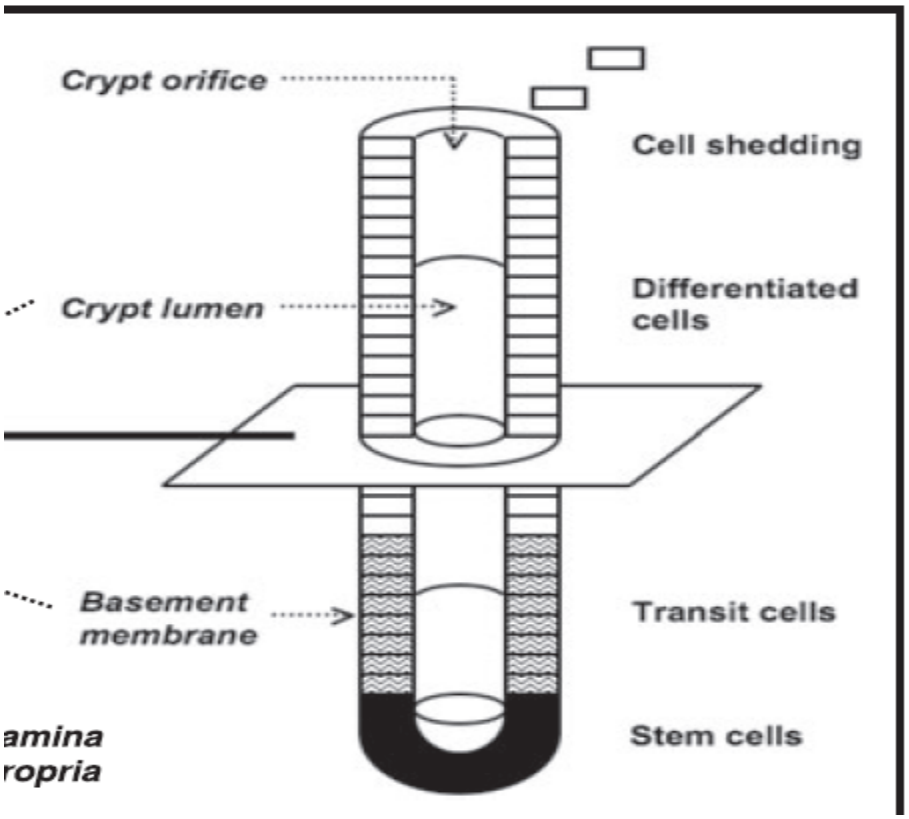
- Spatial model of intestinal crypt
- The model considers the proliferation of basal pinned crypt stem cells and their eventual movement towards the gut

Cell Prolif. 2009, **42**, 617–636 doi: 10.1111/j.1365-2184.2009.00627.x

An integrative computational model for intestinal tissue renewal

I. M. M. van Leeuwen*,†, G. R. Mirams*, A. Walter*, A. Fletcher‡,#, P. Murray‡, J. Osborne§, S. Varma¶, S. J. Young*, J. Cooper§, B. Doyle**, J. Pitt-Francis§, L. Momtahan§, P. Pathmanathan§, J. P. Whiteley§, S. J. Chapman#, D. J. Gavaghan§, O. E. Jensen*, J. R. King*, P. K. Maini‡,††, S. L. Waters‡ and H. M. Byrne*

**School of Mathematical Sciences, University of Nottingham, Nottingham, UK, †Department of Surgery and Oncology, Ninewells Hospital, Dundee, UK, and Department of Microbiology, Tumor and Cell Biology, Karolinska Institute, Stockholm, Sweden, ‡Centre for Mathematical Biology, Mathematical Institute, University of Oxford, Oxford, UK, #Oxford Centre for Industrial Applied Mathematics, Mathematical Institute, University of Oxford, Oxford, UK, §Computing Laboratory, University of Oxford, Oxford, UK, ¶Department of Computer Science, University of Sheffield, Sheffield, UK, **Beatson Institute for Cancer Research, Cancer Research UK, Glasgow, UK, and ††Oxford Centre for Integrative Systems Biology, Department*

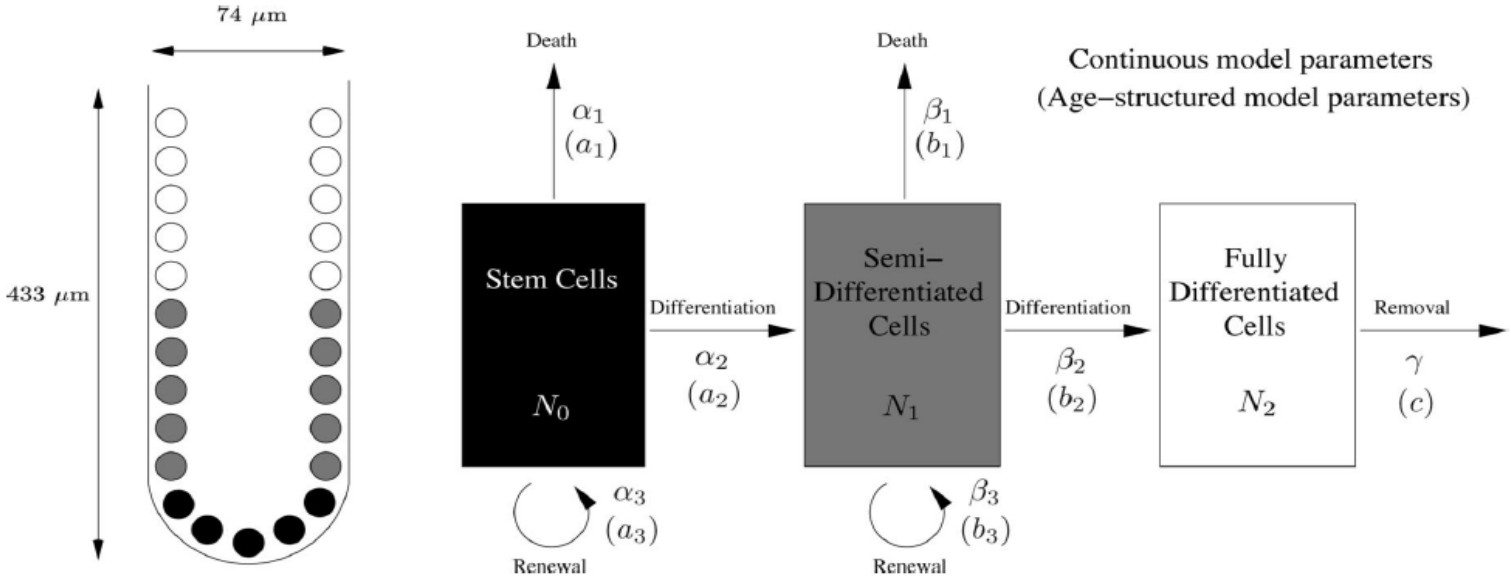


- **CHASTE** free tool
- Bottom shape of the crypt
- Track each cell
- Extracellular signal, intracellular signaling, metabolic pathway – cell division and displacement
- To study epithelial homeostasis in the gut

Mathematical modeling of cell population dynamics in the colonic crypt and in colorectal cancer

Matthew D. Johnston*†, Carina M. Edwards*†, Walter F. Bodmer‡§, Philip K. Maini*¶, and S. Jonathan Chapman†

Centres for *Mathematical Biology and †Industrial and Applied Mathematics, Mathematical Institute, University of Oxford, 24-29 St. Giles', Oxford OX1 3LB, United Kingdom; ‡Cancer Research UK, Cancer and Immunogenetics Laboratory, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Oxford OX3 9DS, United Kingdom; and ¶Oxford Centre for Integrative Systems Biology, Department of Biochemistry, University of Oxford, South Parks Road, Oxford OX1 3QU, United Kingdom



➢Age structured approach that models asynchronous cell division

➢A model to explain the observed lag in colorectal tumour growth.

3.

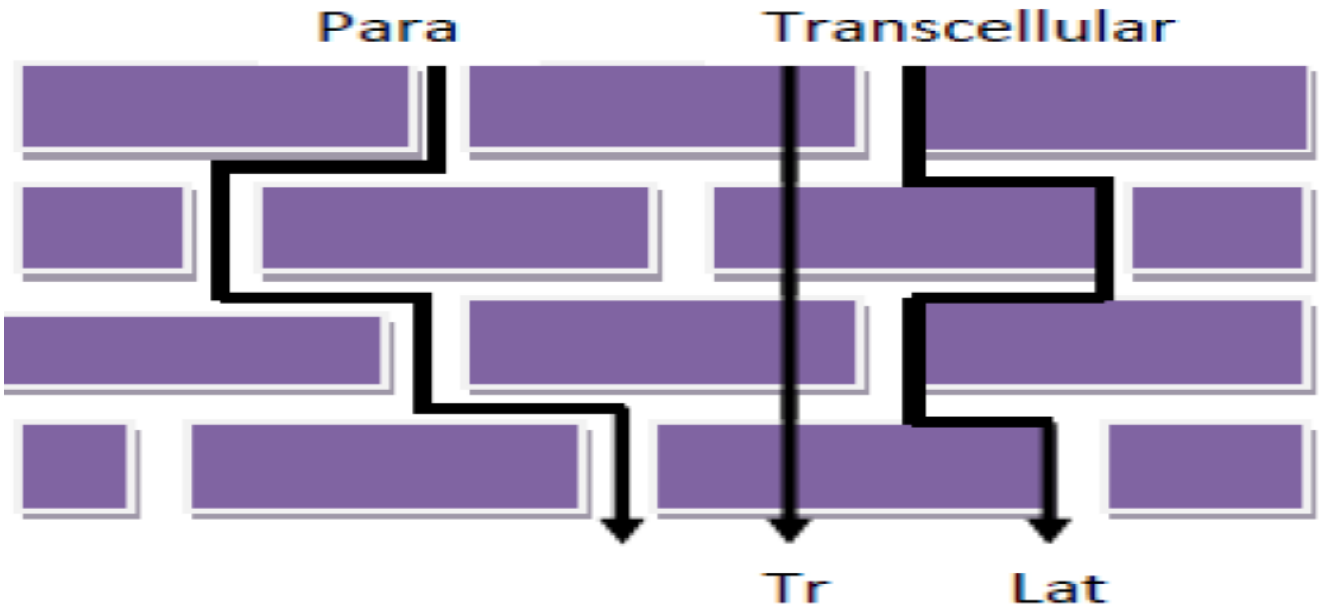
Various models that study and **predict permeability** of epithelium to outside molecules for transdermal **drug delivery**

- Parameters considered of the solute: permeant size, water - octanol partition coefficient , diffusion coefficient
- Parameters considered of the membrane - membrane porosity, membrane tortuosity, membrane thickness.

Potts, R.O. and R.H. Guy, *Predicting skin permeability. Pharmaceutical research, 1992.* ***9(5): p. 663-669.***

Mitragotri, S., *Modeling skin permeability to hydrophilic and hydrophobic solutes based on four permeation pathways. Journal of Controlled Release, 2003.* ***86(1): p. 69-92.***

Edwards, A.l. and M.R. Prausnitz, *Predicted permeability of the cornea to topical drugs. Pharmaceutical research, 2001.* ***18(11): p. 1497-1508.***



- Model **transcellular movement** of large lipophilic molecules:
  - > through epithelial cell membranes (lateral path) and
  - > through the cytosol of the cell (transverse path)
- Hydrophilic and small lipohilic molecules were modeled to pass through intercellular gaps in between the cells - **paracellular movement**

4. Mathematical approach to study the optical properties of the skin

- To derive absorption and scattering coefficients for the stratum corneum.
- To investigate the effect of variation of thickness and melanin content of the corneum in its role of photoprotection
- diffusion model to describe propagation of photon flux in epidermal, dermal and hypodermal layers of the skin.

•Diffey, B.L., *A mathematical model for ultraviolet optics in skin. Physics in medicine and biology, 1983.* ***28(6): p. 647.***

•Dudko, O.K. and G.H. Weiss, *Photon diffusion in biological tissues. Diffusion Fundamentals, 2005.* ***2: p. 114.1-114.21.***

•Schmitt, J.M., et al., *Multilayer model of photon diffusion in skin. JOSA A, 1990.* ***7(11): p. 2141-2153.***

5.

10.1098/rsta.2004.1395

THE ROYAL SOCIETY

Multiscale modelling of human hair

BY REINIER L. C. AKKERMANS AND PATRICK B. WARREN

Unilever Research and Development, Port Sunlight, Quarry Road East, Bebington CH63 3JW, UK (reinier.akkermans@unilever.com)

Published online 2 June 2004

- Used Molecular dynamics to study hair mechanics.
- Their mechanical model predicts a linear decrease of the yield stress with temperature.

Ref: Koh, C.K. and Z. Huang, ***A simple physics model to animate human hair modeled in 2D strips in real time, in Computer Animation and Simulation***. *2001, Springer. p. 127-138.*

- Simple physics model to animate human hair by grouping hair strands into strips.
- To understand the structural and mechanical properties of hair.

Studies are also carried out by keeping in focus the outlook towards hair styling and hair removal. Kolinko and Littler have presented a mathematical model to predict and optimize laser hair removal

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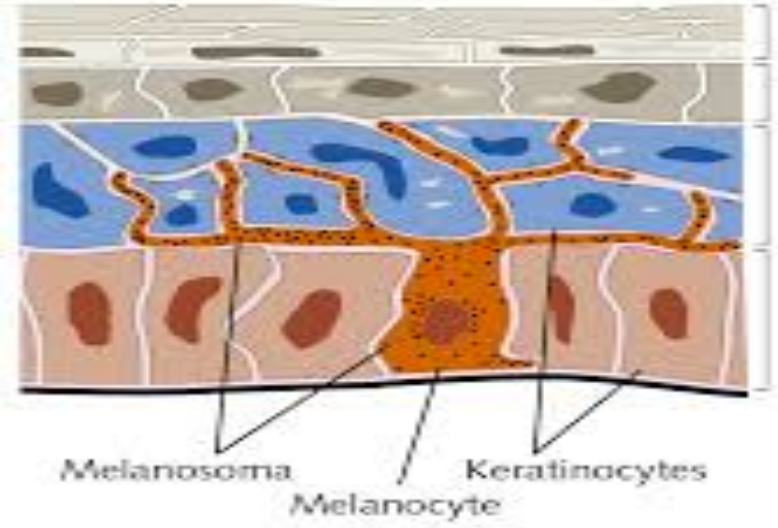
- Preliminary Work

Melanocyte



- Melanocytes comprise from 5% to 10% of the cells in the basal layer of epidermis
- Pigment producing dendritic cells and contain melanosomes
- Skin destined melanocytes are derived from neural crest precursor cells called as melanoblasts.
- Melanoblasts proliferate, differentiate and eventually migrate to stratum basal of the epidermis

Development 138, 3943-3954 (2011) doi:10.1242/dev.067447

Biological and mathematical modeling of melanocyte development

Flavie Luciani[1,2,3], Delphine Champeval[1,2,3], Aurélie Herbette[1,2,3], Laurence Denat[1,2,3], Bouchra Aylaj[4], Silvia Martinozzi[1,2,3], Robert Ballotti[5], Rolf Kemler[6], Colin R. Goding[7], Florian De Vuyst[4,8], Lionel Larue[1,2,3,*,‡] and Véronique Delmas[1,2,3,*,‡]

➢Mathematical model reflecting the main cellular mechanisms involved in melanoblast expansion, including proliferation and migration from the dermis to epidermis

➢The model allows for the calculation of doubling times for melanoblasts of dermal and epidermal melanoblasts

➢The model predicts the number of founder melanoblasts and studies the gain and loss of function of beta catenin in melanoblast expansion

➢The model reveals novel links between cell division, cell localization within the embryo and appropriate feedback control through b-catenin

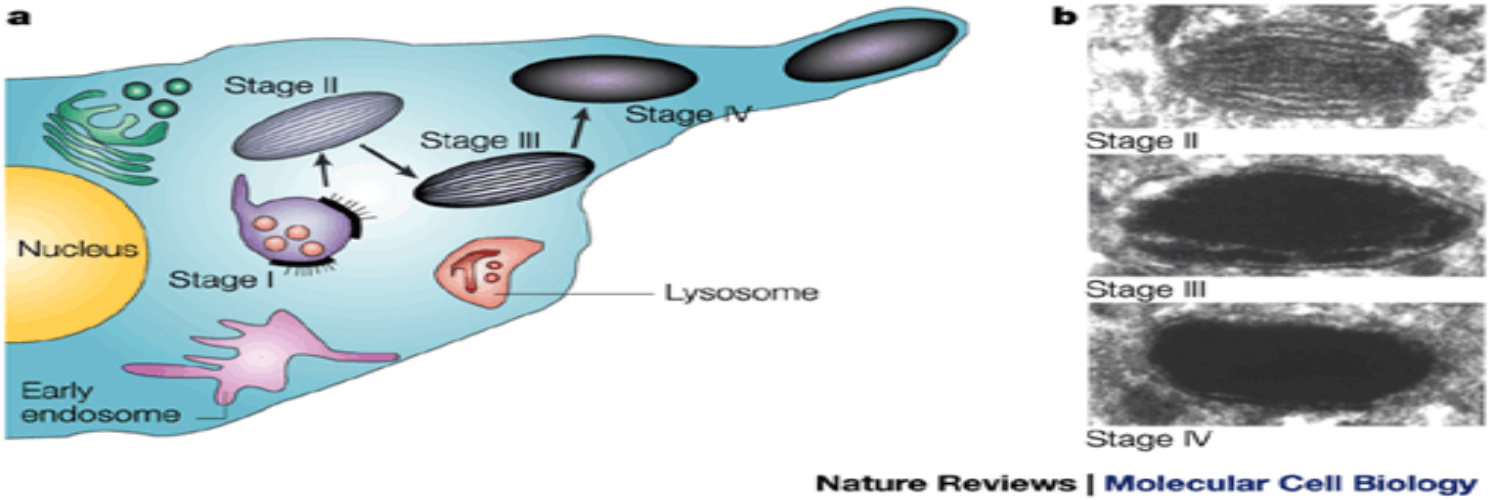
Density of melanocytes

- Density at particular body site same in all skin types
- But intra variation in melanocyte density at different body sites of same individual is observed
- At normal conditions skin melanocytes proliferate slowly and are resistant to apoptosis because of high expression of BCL2
- Constitutive melanocyte density in the skin can be affected by the exposure of skin to harmful ultraviolet light or to toxic chemical compounds

Melanocyte specific organelle
MELANOSOME

- Melanosome maturation
- Melanosome migration
- Nuclear capping

Melanosome maturation



1. Stage I premelanosomes – lack tyrosinase activity and have no internal structural components
2. Stage II melanosomes expresses Tyrosinase and a structural protein Pmel17.
3. Stage III melanosomes are marked by synthesis of melanin and its uniform deposition on internal fibrils.
4. Stage IV melanosomes are fully melanized and ready to be transported

Ref: Marks, M.S. and Seabra.M. C, *The melanosome: membrane dynamics in black and white.* Nature Reviews Mol Cell Bio *2001*

Melanosome transfer into keratinocytes

•Melanosomes are transported from the melanocytes to the neighboring keratinocytes of basal and spinosum layer.

•One melanocyte is observed to pass on the melanosomes to 36 neighboring keratinocytes.

Melanin transfer in human skin cells is mediated by filopodia—a model for homotypic and heterotypic lysosome-related organelle transfer

Suman K. Singh,* Robin Kurfurst,† Carine Nizard,† Sylvianne Schnebert,† Eric Perrier,† and Desmond J. Tobin*,1

*Centre for Skin Sciences, School of Life Sciences, University of Bradford, Bradford, West Yorkshire, UK; and †LVMH Recherche, Saint Jean de Braye, France

Proposed mechanism of melanosome uptake

- cytophagocytosis
- filipodial mediated melanosomal transfer
- discharge of melanosomes into extracellular space and their subsequent uptake by phagocytosis

Traffic 2006; 7: 769–778
Blackwell Munksgaard

doi: 10.1111/j.1600-0854.2006.00425.x

Review

The Quest for the Mechanism of Melanin Transfer

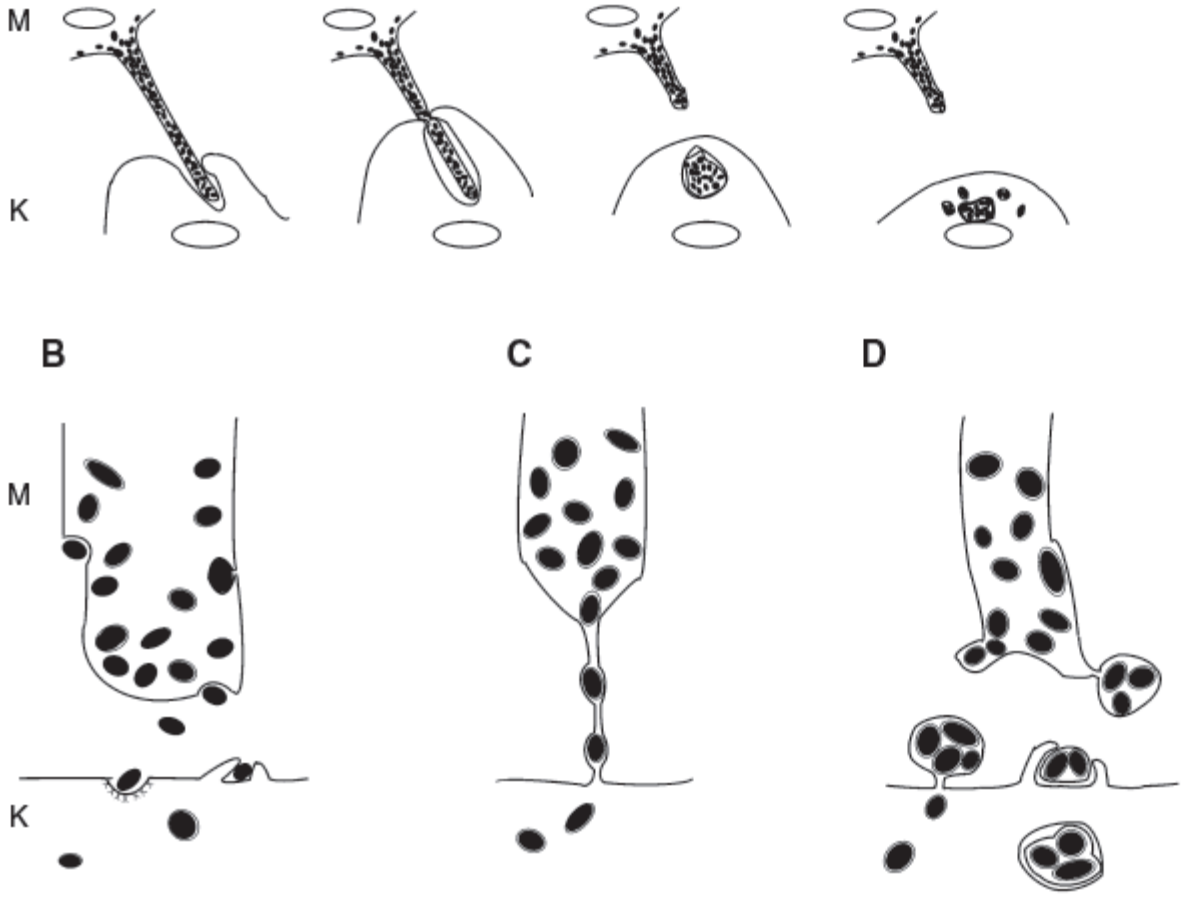
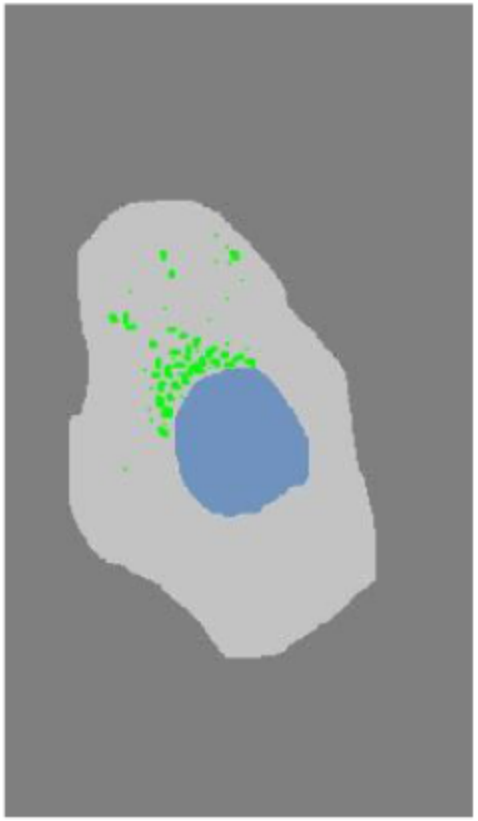


Figure 1: Different modes of melanin transfer. (A) Cytophagocytosis: a melanocytic dendrite is pinched off and phagocytosed, leading to a phagolysosome from which melanin granules disperse throughout the cytoplasm. (B) Exocytosis: melanin is externalized by fusion of the melanosomal membrane with the plasma membrane and is then taken up by endocytosis or phagocytosis. (C) Fusion: plasma membranes of both cells merge creating a channel which allows passage of melanosomes. (D) Membrane vesicles: melanosomes are shed in vesicles which either fuse with the keratinocyte plasma membrane or are ingested by phagocytosis. M: melanocyte, K: keratinocyte.

Distribution of melanosomes in the keratinocytes

- Melanosomes transferred into the keratinocytes cap the keratinocyte's nucleus – nuclear capping.
- The distribution of melanosomes in the keratinocytes is believed to be dependent on size of the melanosomes.
- Large sized melanosomes are singly dispersed in the keratinocytes
- While the smaller sized melanosomes tend to cluster into aggregates



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Variation in skin color

Fitzpatrick classified human skin in 6 classes depending upon its response to UV

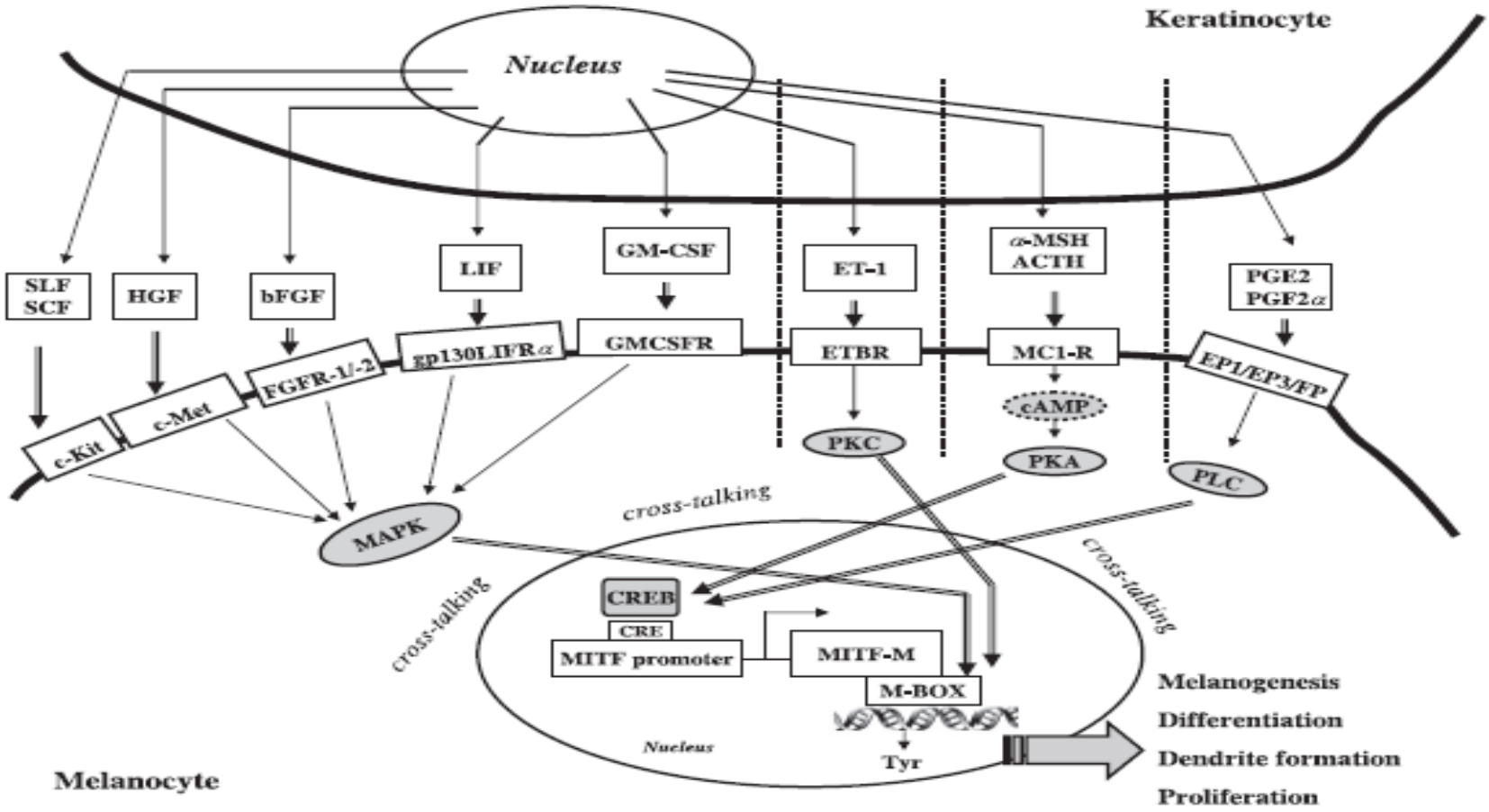
- Constitutive appearance of skin color is effect of total melanin content, melanin composition and the melanosomal size and distribution.
- Surface microtexture and the sebum in the skin affects the reflective property of the skin and hence has an impact on the final appearance of skin color

Models to predict skin color

- Various mathematical techniques like regression analysis, neural networks and image analysis are developed for human skin to predict the color.

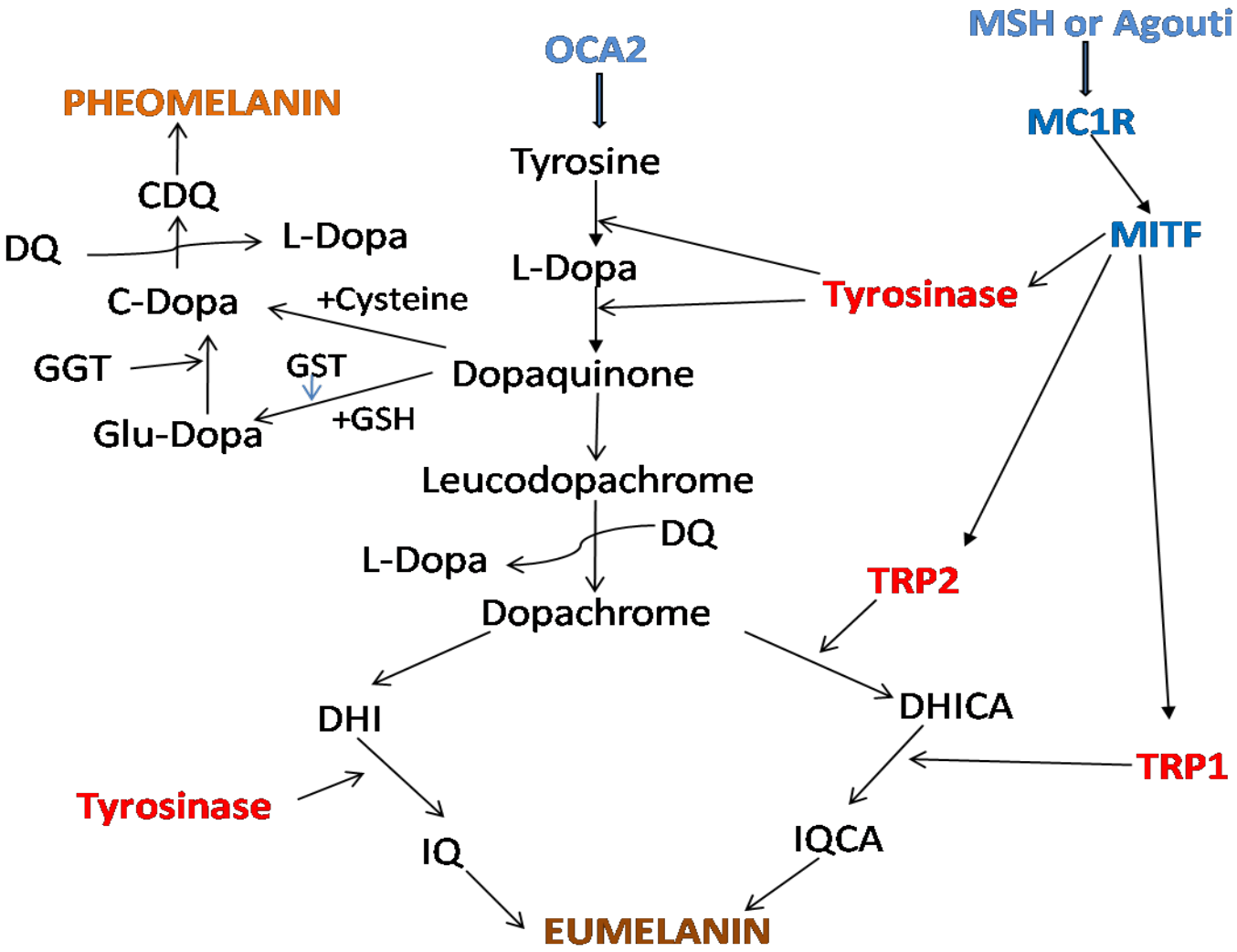
- Reaction diffusion model by Turing (in 1952) to explain the color patterns observed in skin of animals.

Signaling pathways within the melanin unit



Ref: Costin, G.-E. and V.J. Hearing, *Human skin pigmentation: melanocytes modulate skin color in response to stress. The FASEB Journal, 2007.* ***21(4): p. 976-994.***

Melanin synthesis



Light colored alkali soluble melanin: pheomelanin, DHICA containing eumelanin
Dark colored alkali insoluble melanin: DHI containing eumelanin

J. theor. Biol. (2002) **215**, 449–468
doi:10.1006/jtbi.2001.2521, available online at http://www.idealibrary.com on IDEAL®

The Regulatory Basis of Melanogenic Switching

LEIV ØYEHAUG*, ERIK PLAHTE*, DAG I. VÅGE† AND STIG W. OMHOLT†‡

**Department of Mathematical Sciences, P. O. Box 5035, Agricultural University of Norway, 1432 Ås, Norway and † Department of Animal Science, P. O. Box 5025, Agricultural University of Norway, 1432 Ås, Norway*

- A mathematical model to understand the switch between eumelanin and pheomelanin production depending upon an extracellular signal.
- The results supported Ito's hypothesis that melanogenic switching is due to covalent binding of the intermediate dopaquinone to the enzyme glutathione reductase.
- Their results also suggested that the melanogenic switching maybe due to two stable production pattern states because of bifurcation in betweeen the tyrosinase activity .

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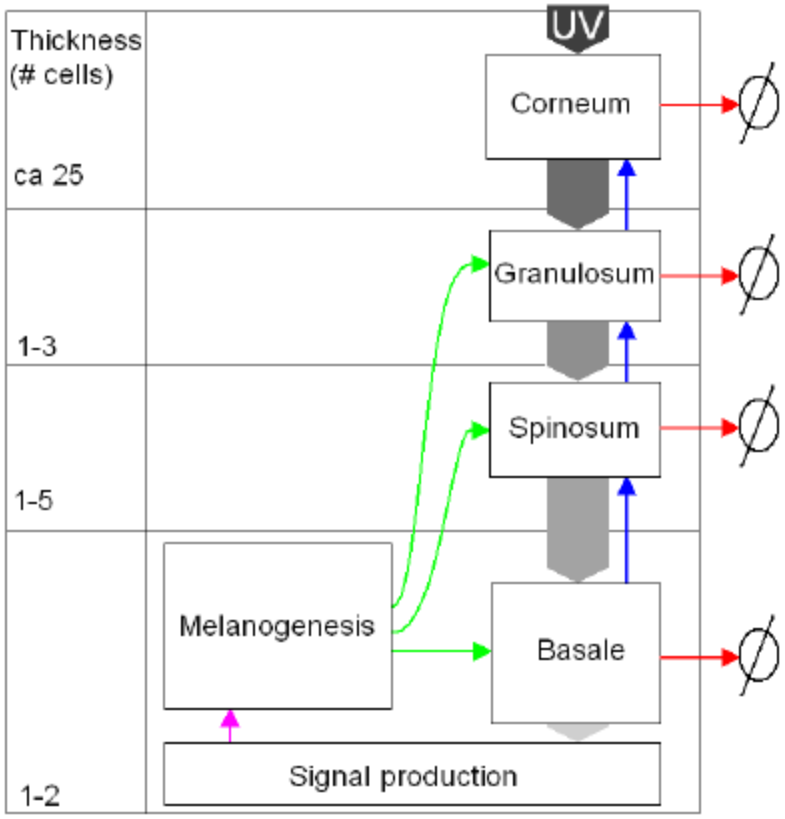
Facultative pigmentation - tanning

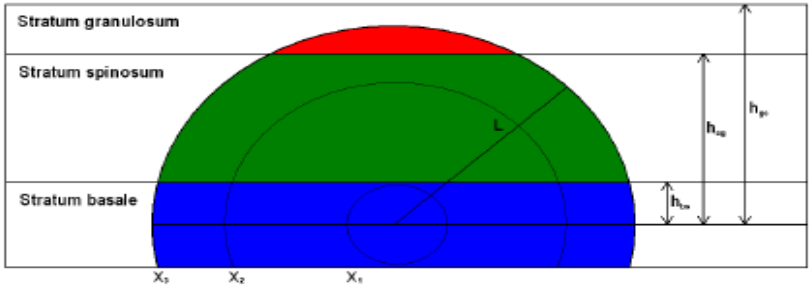
Skins' exposure to UV shows 4 distinctive stages in the pigmentation response as reported in :

1. Immediate pigment darkening (IPD) develops minutes after UV exposure and can remain for several hours. This step is marked by darkening of skin because of oxidation or cyclization of existing melanin.
2. Persistent pigment darkening (PPD) occurs within hours and remains for several days. During ths phase melanosomes migrate to the upper layers of the epidermis and slight increase in melanin content.
3. Delayed pigmentation (DP) develops in days and remains for weeks and is marked increase in melanin content due to newly synthesized melanin.
4. Long-lasting pigmentation (LLP) which remains even for more than 9 months after initial UV exposure.

Ref: Coelho, S.G., et al. *Short-and long-term effects of UV radiation on the pigmentation of human skin. in Journal of Investigative Dermatology Symposium Proceedings. 2009: Nature Publishing Group.*

Josef, T., et al., *The mathematics of tanning. BMC Systems Biology, 2009.* ***3.***





- Model considers a constant external signal activating melanin synthesis.
- Melanin as a species, at the constitutive levels, was modeled to be transported only to the basal layer.
- The model considers melanocyte dendrite lengthening upon UV exposure and the outward movement of the four epidermal layers.
- Volume of sphere was used to calculate the amount of melanin distributed in lower two epidermal layers by the dendrite after the UV stimulus

Outline of the presentation

- ✓ Human Skin
- ✓ Epidermis
- ✓ Melanocytes
- ✓ Constitutive pigmentation
- ✓ Facultative pigmentation
- **Proposal**
- Preliminary Work

Questions that we will try to answer by the model

1. How is the coloring pigment catabolized in the system?
2. How the tanned skin returns to its basal color? The mechanisms involved in melanin degradation are yet not known.
3. Also the mechanisms for long lasting pigmentation remain unresolved.

Multiscale model of human skin epidermis

- Melanocyte unit –

  will include transcription and metabolic melanin synthesis steps

- Keratinocyte unit –

  will include differentiating keratinocytes in the 4 epidermal layers using freely available tool CHASTE

- The model will try to answer whether complete epidermal turnover, desquamation (shedding of the stratum corneum) alone can explain detanning .

- The parameter set in the model resulting in continuous higher melanin levels can be analyzed to reason out the persistence of pigmentation in the case of LLP.

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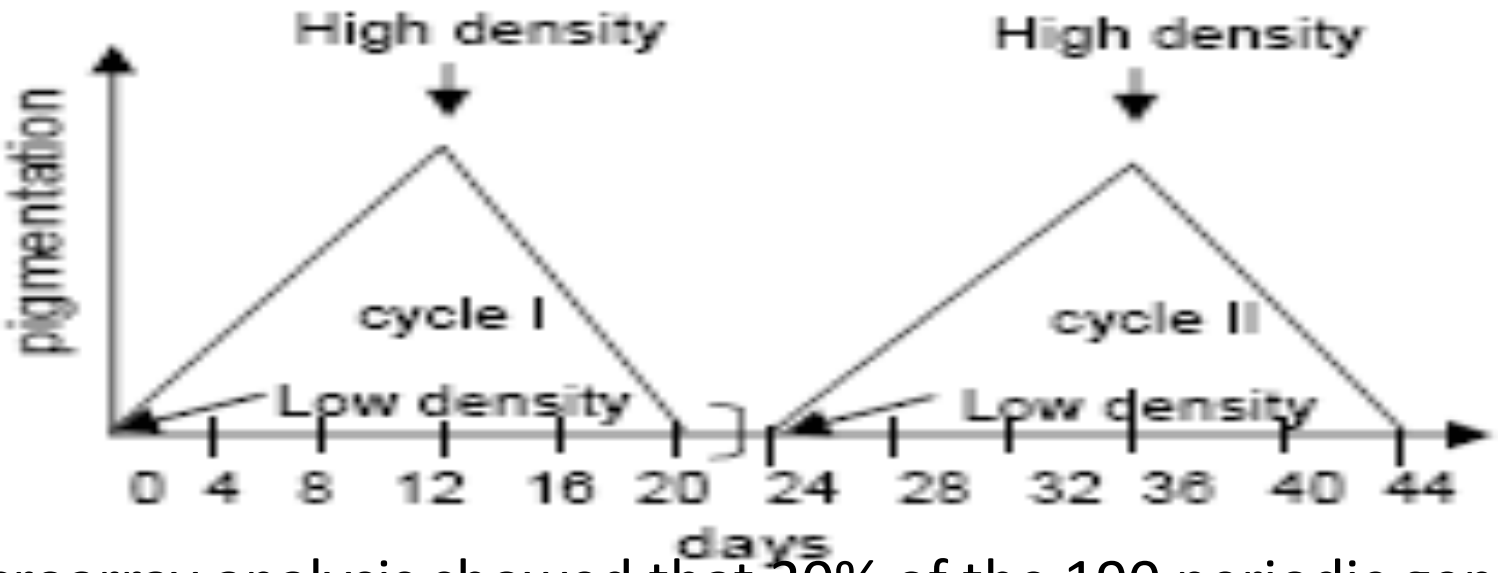
Simple Mathematical Model

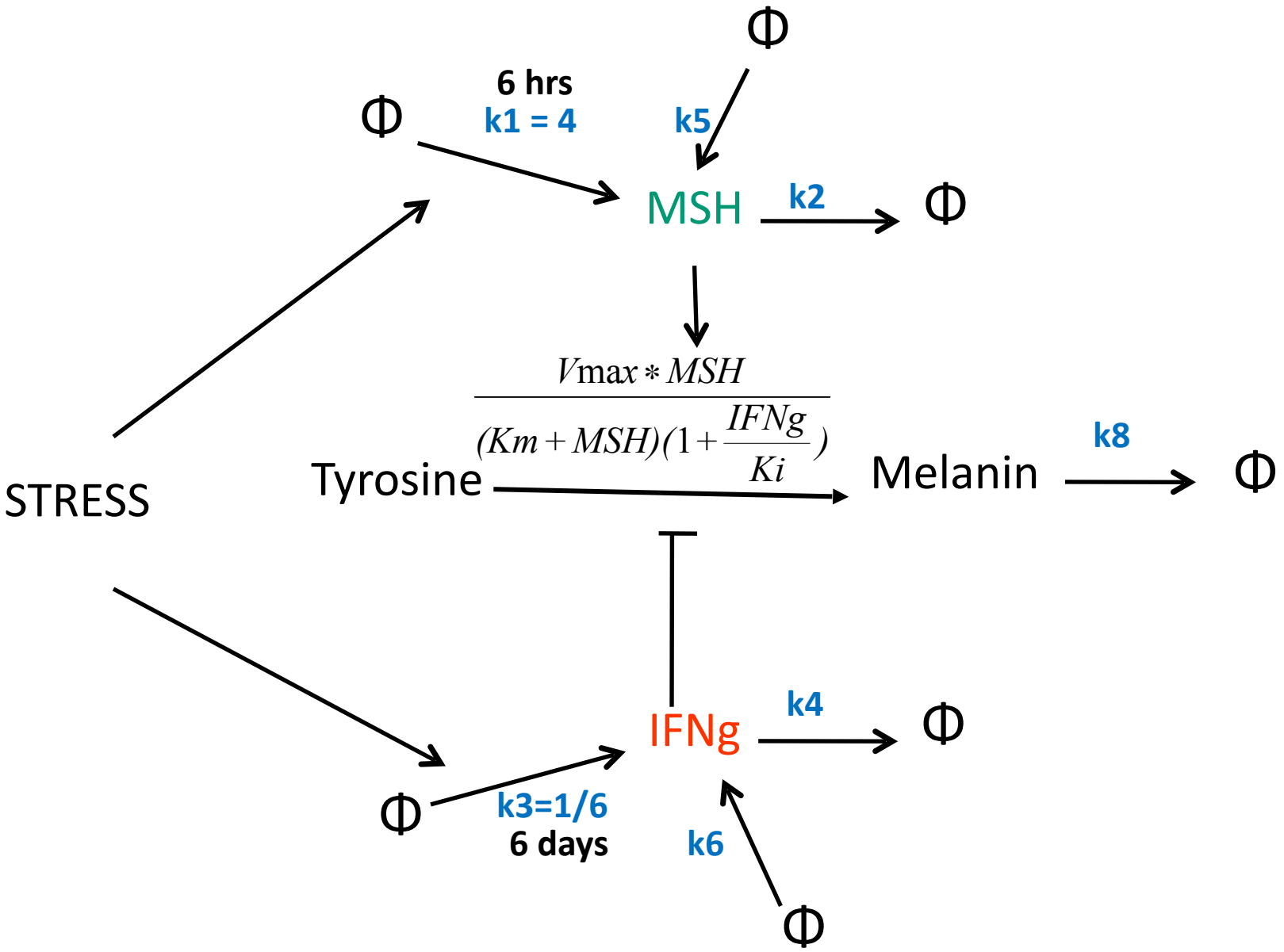
Experimental setup of B16 melanoma cells at IGIB, Delhi

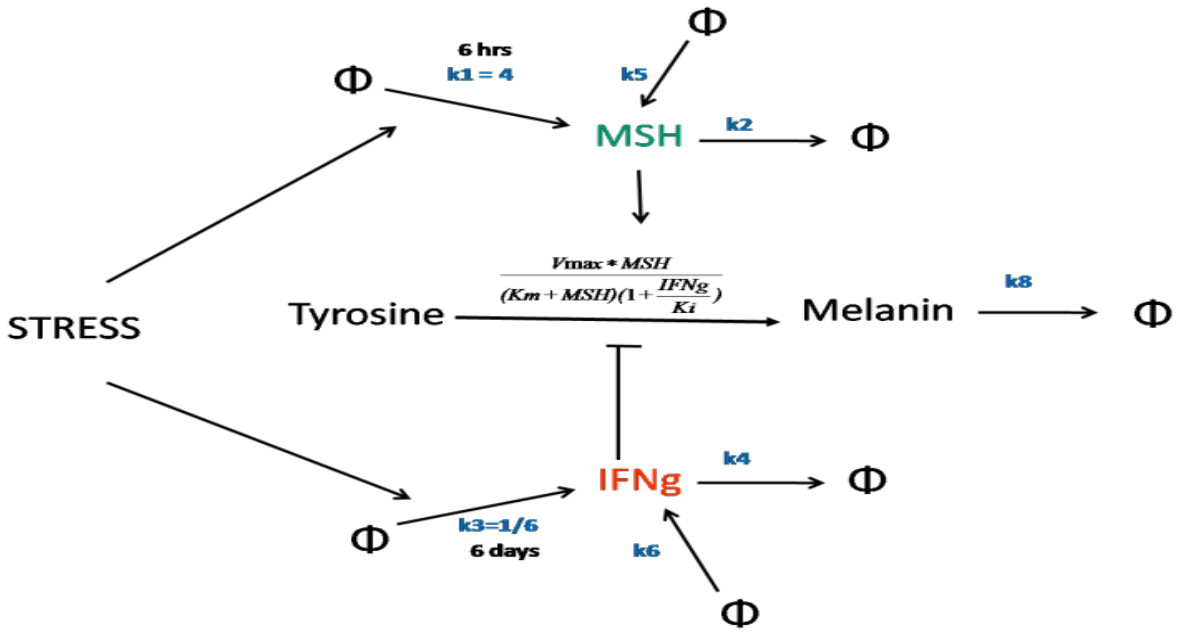


Microarray analysis showed that 20% of the 190 periodic genes have immune related function. The genes were a part of IFNg mediated signal transduction pathway.

Hypothesis: Immune related factors – Interferon gamma activity is involved in depigmentation.

Pictorial representation of the model





$$\frac{d[aMSH]}{dt} = k5 + k1[stress] \quad - k2[aMSH]$$

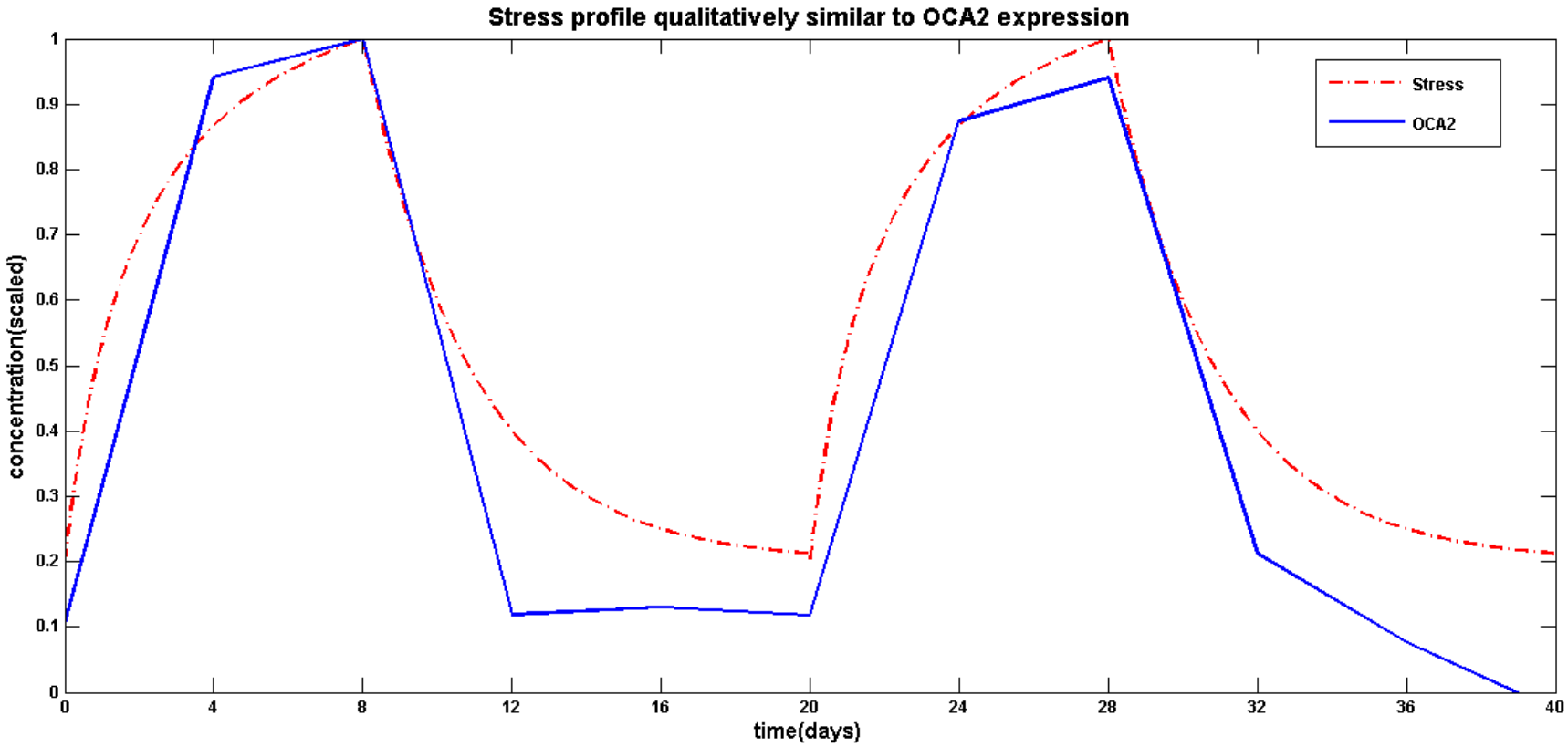
$$\frac{d[IFNg]}{dt} = k6 + k3[stress] \quad - k4[IFNg]$$

$$\frac{d[melanin]}{dt} = \frac{V_{max}[aMSH]}{(K_m + [aMSH])(1 + \frac{[IFNg]}{K_i})} - k8[melanin]$$

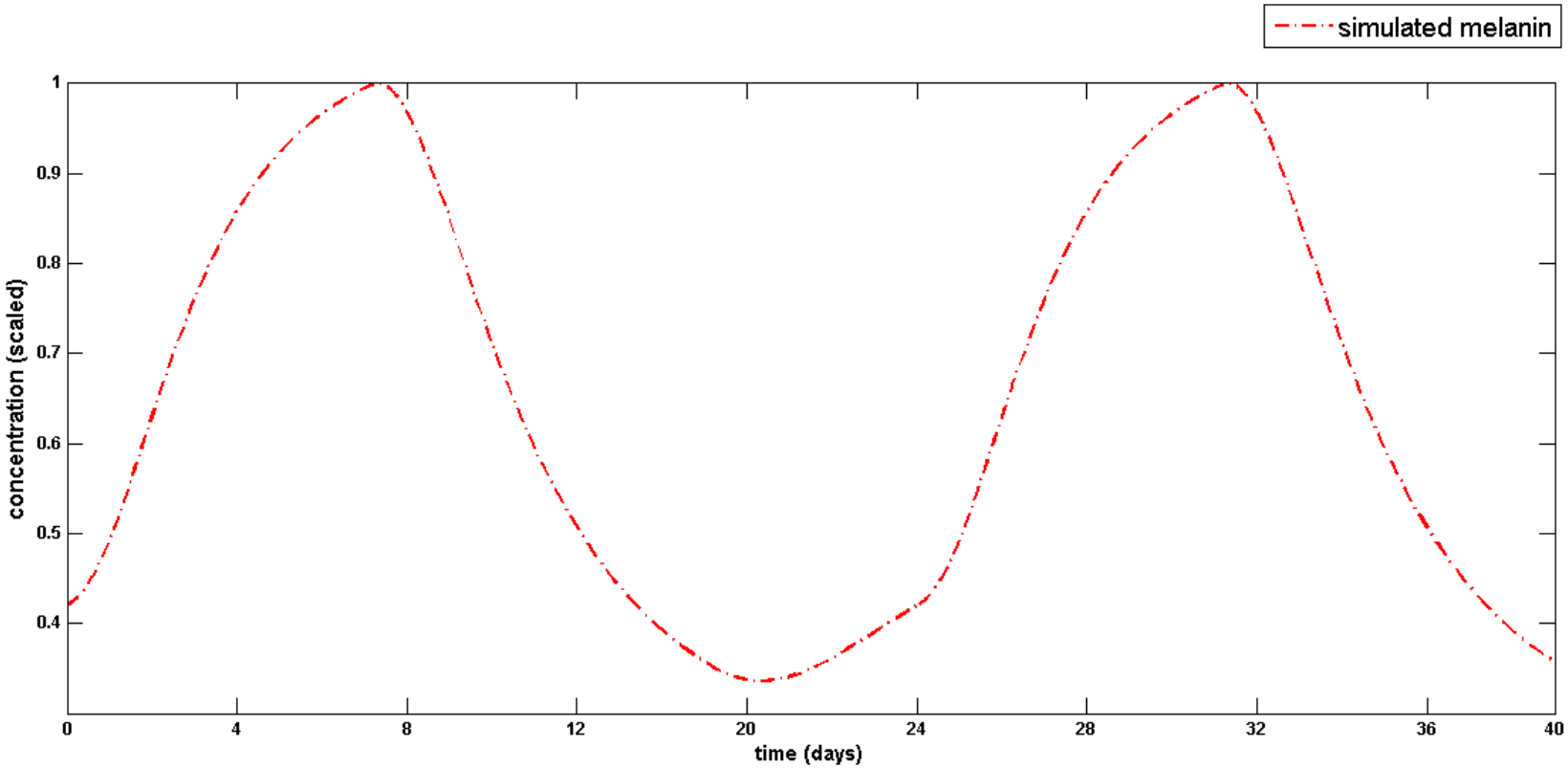
Parameters

Parameter	Parameter Value		Reference
k1	1/0.25 [scaled concentration units] day^{-1}	6 hours	(Cui, Widlund et al. 2007)
k3	0.1667 [scaled concentration units] day^{-1}	6 days	(Cui, Widlund et al. 2007)
k2	1		(Zaidi, Davis et al.)
k6	0	IfnG absent at physiological level	
k5	1		
k4	1		
Km	5 [scaled concentration units]		
Vmax	1 [scaled concentration units]day-1		
Ki	0.1 [scaled concentration units]		
K8	1		

Input ‘Stress’ profile qualitatively similar to the microarray expression of OCA2

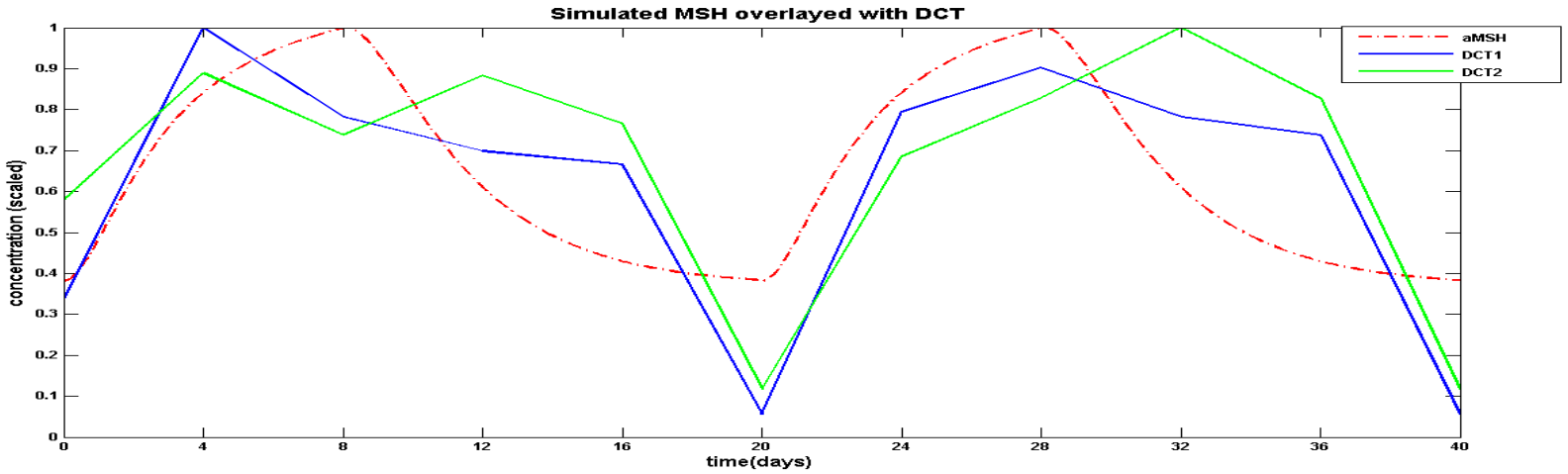


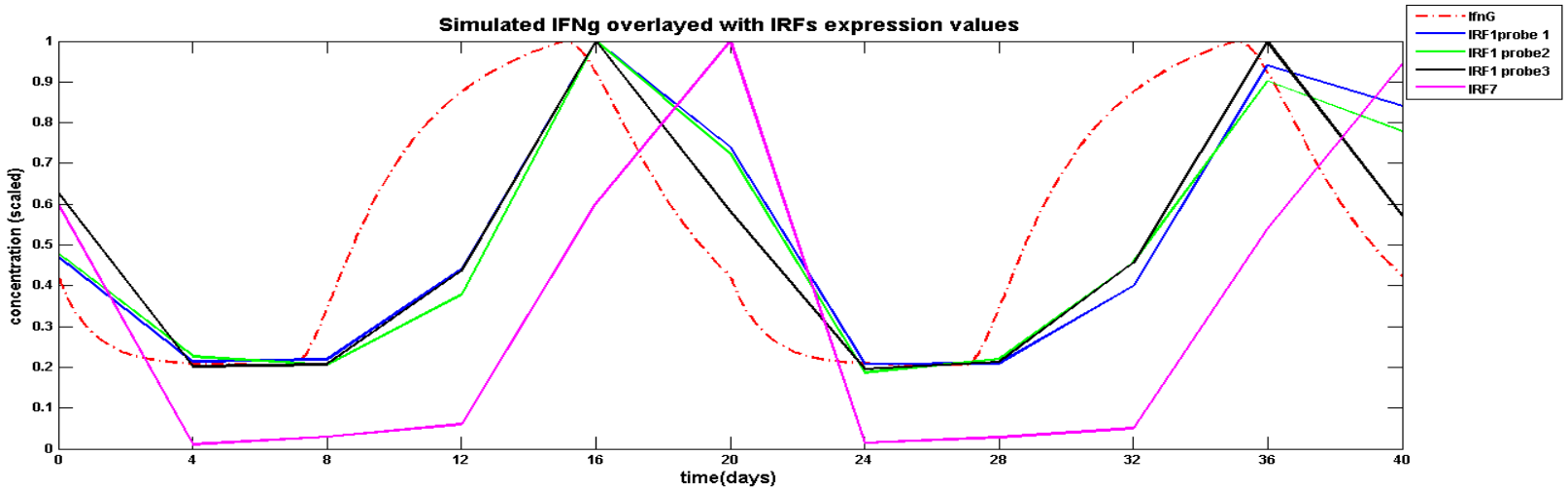
Plot for simulated melanin



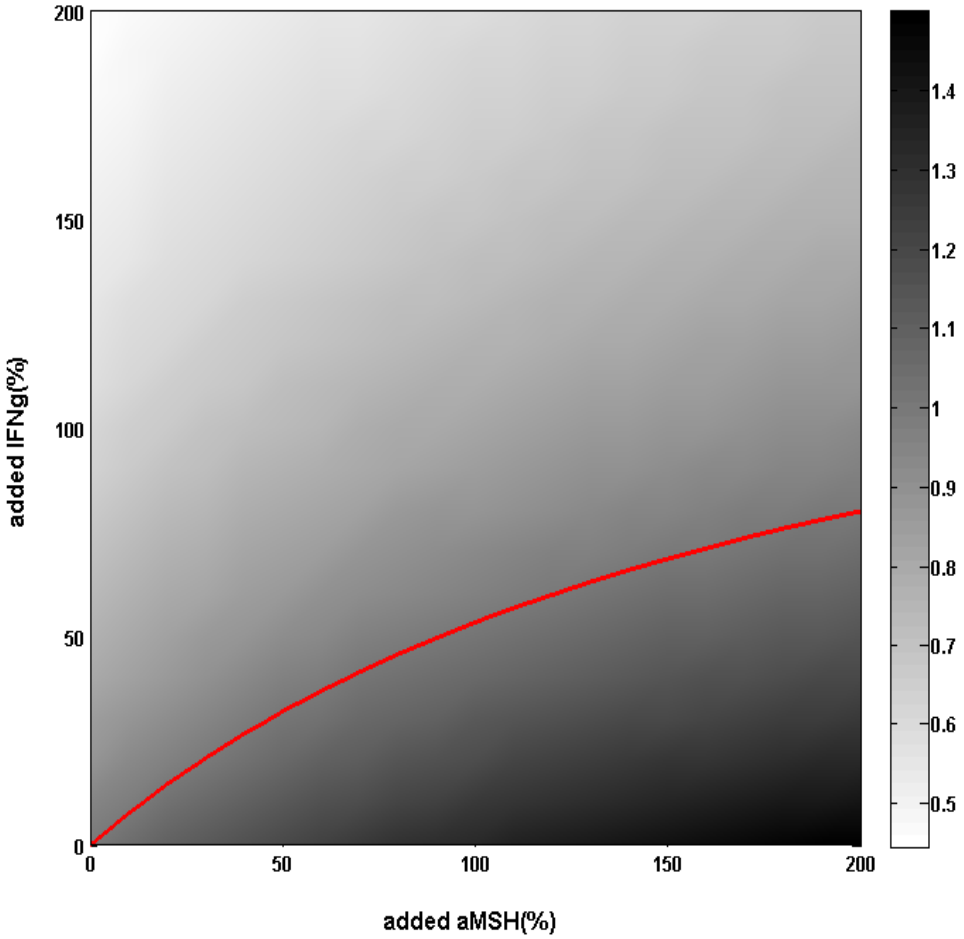
Simulated melanin having expression qualitatively similar as experimentally observed pigmentation

Plot for simulated MSH and IFNg





Varying MSH and IFNg



Surface plot of scaled melanin concentration

The added α-MSH and IFN-γ are as a fraction (from 0-200%) of their respective amounts that is present due to the stress in the absence of any external additions.

Thank you!