

Skin Disease Modeling from a Mathematical Perspective

Reiko J. Tanaka¹ and Masahiro Ono^{2,3}

Mathematical modeling is a promising approach to reveal disease-related regulatory mechanisms. This article gives an overview of how mathematical modeling can increase our understanding of skin disease, addressing both its benefits and challenges. We discuss the importance of strong links among experiments, mathematical modeling, and data analysis in order to effectively use the modeling approach to advance skin research in the postgenomic era. Investigative dermatologists are needed to drive and orient this cross-disciplinary research to address fundamental problems in skin biology and disease.

Journal of Investigative Dermatology (2013) **133**, 1472–1478; doi:10.1038/jid.2013.69; published online 21 March 2013

INTRODUCTION: WHY A MATHEMATICAL PERSPECTIVE?

The past 20 years have witnessed a dramatic increase in our knowledge of the molecular mechanisms of skin diseases, leading to improvements in diagnosis and treatment (O'Toole, 2010; Uitto *et al.*, 2012). Technological advances, such as microarray and deep sequencing for transcriptomic analysis, enable simultaneous quantitative measurements of the expression and activity of effectively all the components in the tissue (Ideker *et al.*, 2001) in normal and disease conditions (Strohmman, 2002). However, these quantitative measurements are snapshots and only capture a small part of the entire process. How are these snapshots related to each other and how does the amount of each molecule change over time?

Skin is a highly dynamic tissue with continually renewing epidermis and ever-surveilling immune cells. Appropriate functioning of the regulatory mechanisms built into the system maintains homeostasis, and malfunction of the regulatory mechanisms may result in disease. Understanding the disease state is thus equivalent to understanding the disease-related regulatory mechanisms. *Mathematical modeling* offers a means

for understanding and describing these dynamic regulatory mechanisms (Vodovotz *et al.*, 2008; Auffray *et al.*, 2009; Hunter and Viceconti, 2009). Mathematically explicit and quantitative descriptions of the dynamics of the system, coupled with experiments, can reveal hidden regulatory mechanisms that cannot be revealed by conventional experimental methods. Mathematical models will also be useful for personalized treatments in future. For example, model simulation using the data of an individual patient at several times may effectively reveal the characteristics of the patient and enable optimal administration of drugs for the treatment of malignant tumor and viral infection (Cambiano and Phillips, 2011; Luo *et al.*, 2011; Hirata *et al.*, 2012).

STEPS TO MODEL SKIN DISEASE FROM A MATHEMATICAL PERSPECTIVE

This section illustrates the different steps in the modeling approach, with a mathematical model of atopic dermatitis (AD) (Tanaka *et al.*, 2011), designated as “the AD model” hereafter, as a specific example (Figure 1). Although we focus on the modeling from

the control engineering perspective, the most effective modeling approach may vary for each biological problem.

Definition of the target and hypothesis

Modeling skin disease begins with defining the system to be modeled and the hypothesis to be examined. This step requires a sufficient knowledge of both experimental systems and modeling methods, and collaboration between experimental researchers and mathematical modelers is indispensable from the very beginning, as biological knowledge of the target disease is essential to identify the subsystems to be modeled. The modeling approach is most effective in revealing the regulatory relationships among well-characterized molecules and in analyzing general features of a skin disease.

The AD model was developed to reveal the regulatory mechanism for the barrier homeostasis and its relation to inflammation in AD. We defined the hypothesis that a positive feedback mechanism that regulates the activity of protease kallikreins (KLKs) produces the outbreak and persistence of inflammation in AD (Figure 1a), based on the observations that barrier dysfunction and immune dysregulation contribute

¹Department of Bioengineering, Imperial College London, London, UK; ²Institute of Child Health, University College London, London, UK and ³Department of Dermatology, Kyoto University, Kyoto, Japan

Correspondence: Reiko J. Tanaka, Department of Bioengineering, Imperial College London, London, SW7 2AZ, UK. E-mail: r.tanaka@imperial.ac.uk or Masahiro Ono, Immunobiology Unit, Institute of Child Health, University College London, 30 Guilford Street, London, WC1N 1EH, UK. E-mail: m.ono@ucl.ac.uk

Abbreviations: AD, atopic dermatitis; KLK, kallikrein; LEKTI, lympho-epithelial Kazal-type-related inhibitor; PAR2, protease-activated receptor 2

Received 27 July 2012; revised 23 November 2012; accepted 11 December 2012; published online 21 March 2013

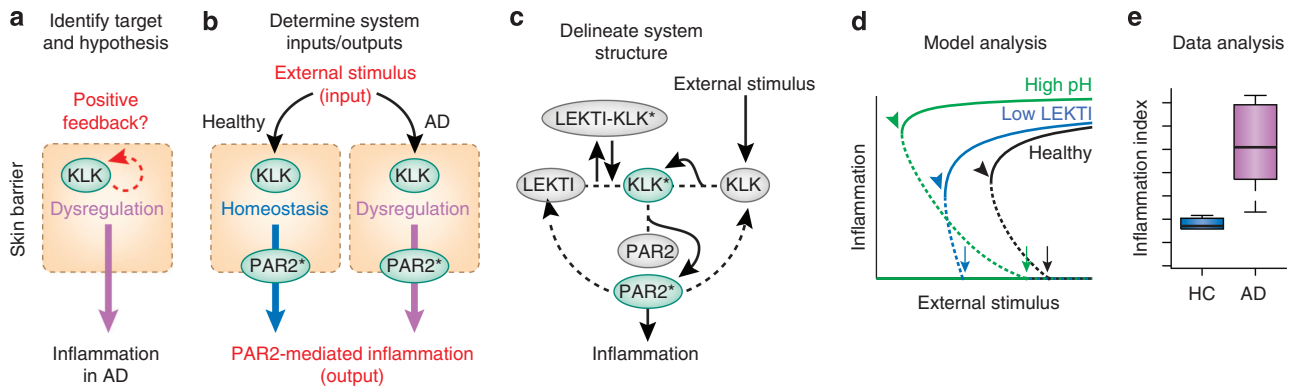


Figure 1. Key steps in mathematical modeling of atopic dermatitis (AD). (a) A target of the modeling was identified as the regulatory system of kallikrein (KLK) activity. A hypothesis was formed that a positive feedback mechanism that regulates KLK activity captures the essential features of AD. (b) The systems inputs and outputs were determined. In this case, external environmental stimuli are the inputs that lead to KLK activation. In normal healthy homeostasis, the output is a disease-free state, whereas in AD, excessive activation of KLKs leads to inflammation. (c) The minimal network of interactions between the KLK inhibitor LEKTI (lympho-epithelial Kazal-type-related inhibitor), KLKs, and protease-activated receptor 2 (PAR2) was described by a simple diagram as shown, and were translated into a system of ordinary differential equations. This comprised the mathematical model. KLK* and PAR2* represent the activated forms of KLK and PAR2, respectively. (d) The relationship between the input (external stimulus, abscissa) and the output (PAR2-mediated inflammation, ordinate) was obtained by bifurcation analysis of the model using computer simulation. The solid lines show the observable inflammation levels given the external stimulus. This model analysis indicates the characteristic features of inflammation in AD patients (here defined by high pH or lower LEKTI): the levels of external stimulus (x-axis) that lead to the outbreak of inflammation are lower in AD patients than in healthy controls (shown by arrows), and the external stimulus has to be reduced further in AD patients (shown by arrowheads) to obtain an inflammation-free status. (e) Microarray data of AD and healthy skin samples were analyzed to create an index for the level of PAR2-mediated inflammation. AD patients showed higher scores compared with healthy controls (HC; box plot). The microarray results and the model results were compared to refine the hypothesis.

to the development of AD (Denda *et al.*, 1998; Leung, 2000; Cork *et al.*, 2009) and that the excessive activity of KLKs increases skin desquamation, resulting in barrier dysfunction and eczema (Voegeli *et al.*, 2009).

Model development

Determine the system outputs and inputs. To develop a mathematical model, the outputs and inputs of the system should be clearly identified. The outputs correspond to the major outcome of the dysregulation of the system that drives the disease process. They correlate with disease activity and are primarily monitored for the disease treatment. Generally, the inputs trigger the disease activity through the internal regulatory mechanisms, although the symptoms can also be triggered without explicit inputs but by internal dysregulation. The output and the input of the AD model were defined as the inflammation mediated by protease-activated receptor 2 (PAR2) and the external stimulus that triggers the inflammation, respectively (Figure 1b), as KLKs activate PAR2 on the surface of keratinocytes causing inflammation (Rattenholl and Steinhoff, 2003; Cork *et al.*, 2009) and PAR2 activation is the most proximal to epidermal dysregulation in a series of inflammatory events.

Determine the system structure for regulatory mechanisms. The model structures (e.g., mechanistic and physical interactions between the components) are determined based on previous biological studies. Obviously, the model should include the key components so that the model results are clinically or biologically relevant and can be compared with experimental results. Models should be as simple as possible, yet as complex as necessary to address the specific question of interest (Garny *et al.*, 2005). This tradeoff determines the difficulty in validation, analysis, and interpretation. The AD model includes a protease inhibitor of KLKs, lympho-epithelial Kazal-type-related inhibitor (LEKTI), because it is a causal gene of a genetic skin disease, Netherton syndrome, and the uncontrolled KLK activity in Netherton syndrome epidermis triggers AD-like lesions (Briot *et al.*, 2009). The AD model contains a minimal number of components, avoiding unnecessary complexity, while still capturing the essential characteristics of inflammation in AD (Figure 1c).

Translate into mathematical description and find parameters. Regulatory mechanisms can be described by different mathematical tools, including differential equations, agent-based models, Petri nets,

and cellular automata (Materi and Wishart, 2007; Machado *et al.*, 2011). The most effective tool varies for each biological problem. The value ranges for model parameters, such as decay rates and reaction rates, should be estimated by the experimental data. For the AD model, the reactions and interactions between KLKs, PAR2, and LEKTI were translated into ordinary differential equations and the value ranges for the parameters were taken from the literature.

Model analysis

Once the model is developed, its analysis is carried out mathematically. Ideally, the model will predict the future behavior of the system, identify the possible dysregulation points (i.e., changes in model structures and parameters), predict the effects of interventions, and test conditions that are difficult to be realized experimentally.

For example, *bifurcation analysis* is an analytical method to investigate the relationship between parameter values and the steady states (the state that the system reaches after long time; e.g., when drug effects are stabilized). *Time course analysis* by computer simulation may reveal nonintuitive dynamics of each component in the system.

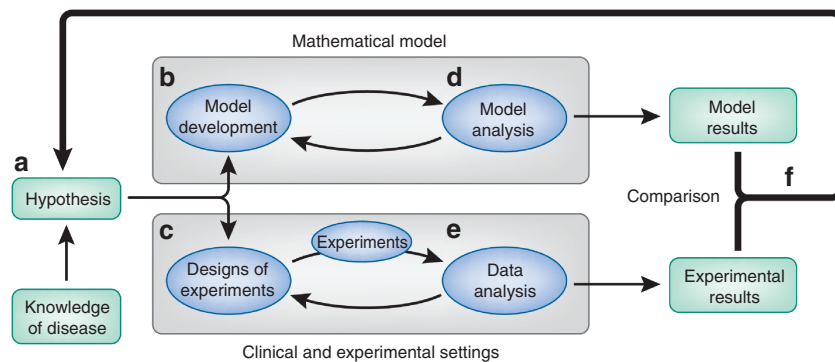


Figure 2. An integrative approach of experiments and modeling for skin disease. (a) Based on the available experimental data and knowledge of the disease in question, a hypothesis is formed and systems to be modeled are identified. (b) A mathematical model to test the hypothesis is developed, by describing clinical and experimental data on key components by mathematical terms. (c) Experiments are designed to obtain data required to determine key parameters and to be compared with the model. The feasibility of experiment is a major factor that constrains the model structure. (d) The developed model is mathematically analyzed to provide a set of model results. Iterations of model development and model analysis refine the model, whose results should be compared with experimental results. (e) Raw experimental data are analyzed and mined for direct comparison with the model results. (f) The model results and the experimental results are compared, and the results are used to refine the original hypothesis and the mathematical model and to identify critical experiments. These processes are repeated to obtain a better understanding of the disease mechanisms.

Parameter sensitivity analysis systematically investigates which parameters have large impacts on the system behavior (Cho and Shin, 2003). *Sensitive* parameters, whose small changes dramatically alter the system behavior, should be carefully measured by experiments, whereas “insensitive” parameters are possible targets for parameter reduction to simplify the model.

Bifurcation analysis of the AD model shows that the model captures the fundamental nature of inflammation: the level of inflammation increases abruptly once the external stimulus exceeds a threshold level (Figure 1d). It also predicts that stronger and more persistent inflammation is triggered by smaller stimulus in atopic conditions (represented by high pH and low LEKTI) as compared with healthy skin.

Data analysis for the comparison of data and model

Disease activity is usually the primary interest in clinical settings, and therefore is the main focus of the model–data comparison. The disease activity is mostly evaluated by a combination of multiple *qualitative* measurements (e.g., visual and histological observations) and *quantitative* measurements of the concentration of key molecules. Full use of both data for direct comparison with the model results requires appropriate

data analysis such as *multidimensional analysis*.

As the output of the AD model, PAR2-mediated inflammation, could not be measured directly, an index created by multidimensional analysis of microarray data was used to compare the model predictions with clinical data (Figure 1e).

Biological interpretation of the results

Finally, the experimental data and model predictions are compared and the results are used to refine the original hypothesis and deepen our understanding of the system. Inconsistencies between the model and experimental results, if found, suggest the need to further refine the model. If adding extra components to the model better explains the experimental data, new experiments may be attempted to explore the unidentified mechanism. If some parameters are critical for fitting the model to the experimental results, new experiments may focus on the mechanism that determines these critical parameters. Meanwhile, the model results may identify unnecessary experimental comparisons or time points.

Analysis of the AD model reveals that feedback regulation of KLK and LEKTI production mediated by PAR2 is critical to determine the level of inflammation. Furthermore, it shows that the balance between the degradation rates of KLK and PAR2 and the feedback strength are

the most important factors in determining the behavior of the system. These key parameters remain to be experimentally measured to further reveal their molecular mechanisms.

This iterative cycle of experiments and modeling is most productive if it raises biologically meaningful questions about the mechanisms that maintain homeostasis and how the disturbances in these mechanisms lead to disease. Figure 2 summarizes the combined approach of experiment and modeling.

IMPACT: WHAT BENEFITS CAN SKIN RESEARCH EXPECT FROM MATHEMATICAL MODELING?

This section examines possible applications of the modeling approach to basic and clinical problems.

Revealing the dynamic mechanisms of the skin

Skin is a dynamic organ and its homeostasis is maintained through the regulation of the differentiation, proliferation, migration, and death of various cells. Here we consider three dynamic systems in the skin: epidermis, hair follicles, and the skin immune system.

Epidermis. The epidermis is a multi-layered epithelium composed largely of keratinocytes, continually renewed by differentiated cells in the basal layer. Keratinocytes show terminal differentiation from stratum granulosum to stratum corneum,

where the skin permeability barrier is formed (Cork *et al.*, 2009; Jepps *et al.*, 2013). Epidermal homeostasis is abrogated in inflammatory diseases involving the epidermis (Lowes *et al.*, 2007; Cork *et al.*, 2009), where dysregulation of the homeostatic mechanisms of keratinocytes can contribute to inflammation, which, in turn, may alter the differentiation of keratinocytes. Mathematical modeling is effective for revealing those complex interacting relationships, and has been applied to psoriasis, as well as our work on AD described in our previous section, with potentially important clinical consequences. Psoriasis is characterized by excessive growth and aberrant differentiation of keratinocytes and inflammation in the epidermis and dermis. The morphology of psoriatic skin has been analyzed by a geometric model (Iizuka *et al.*, 1997) and a computational model of epidermal homeostasis (Grabe and Neuber, 2007). Keratinocytes in psoriatic lesions contribute to inflammation by producing cytokines and chemokines such as IL-8, CCL20, and S100A8/A9 that recruit neutrophils and lymphocytes into the lesions (Lowes *et al.*, 2007; Strange *et al.*, 2010). The polarization of helper T cells in psoriatic lesions between the T helper types 1 and 17 (Lowes *et al.*, 2007; Perera *et al.*, 2012) has been addressed by mathematical modeling (Valeyev *et al.*, 2010). Lymphocyte-derived cytokines, in turn, act on keratinocytes to either induce inflammatory genes or increase proliferation (Lowes *et al.*, 2007; Pastore *et al.*, 2008). As a psoriatic lesion is the manifestation of the interaction between the dysregulation of keratinocyte differentiation and the immune system, clarifying the dynamic interplay between these two systems, in addition to the intrinsic control mechanism in each cellular compartment, is essential and can be effectively addressed by mathematical modeling.

Hair follicles. Hair follicles show the dynamic cycle of epithelial growth (anagen), regression (catagen), and quiescence (telogen) (Stenn and Paus, 2001). Understanding of hair growth disorders, characterized and classified by the patterns of alteration of the hair cycle, can be greatly advanced by mathematical modeling (Al-Nuaimi *et al.*, 2010). A mathematical model was proposed to

address the feedback control mechanism from matrix keratinocytes to the dermal papilla (Al-Nuaimi *et al.*, 2012). Human hair cycles have been analyzed using an automaton model that defines the rule of transition for each hair follicle (Halloy *et al.*, 2000; Plikus *et al.*, 2011). A combination of these approaches will provide new insights into hair growth disorders.

The immune system: skin and systemic. Skin is a dynamic immune organ. The onset of inflammation triggers the flow of immune cells back and forth between the skin and the systemic immune systems: activated keratinocytes and lymphocytes recruit granulocytes and circulating lymphocytes into the skin by producing chemokines (Bos *et al.*, 2005; Nestle *et al.*, 2009); activated dendritic cells migrate to the draining lymph nodes to prime T cells (Nestle *et al.*, 2009); and skin-homing memory T cells traffic to the draining lymph nodes (Egawa and Kabashima, 2011). During these processes, T cells differentiate into helper and regulatory T cells, the pattern of which is thought to determine the nature of the immune response (Sakaguchi *et al.*, 2008; Nestle *et al.*, 2009; Egawa and Kabashima, 2011). The alteration of the immunological environment in the skin has significant impact on the compositions of T cells in the circulation (Loser *et al.*, 2006; Fujii *et al.*, 2011). Mathematical modeling is useful to understand these dynamic events by revealing the cellular kinetics of lymphocytes in the skin and systemic immune systems, depending on their activation and differentiation status. It has been used to reveal the mechanisms of the key steps including T-cell homeostasis (Thomas-Vaslin *et al.*, 2008), chemotaxis (Onsum and Rao, 2007), antigen presentation (Kirschner *et al.*, 2007), T-cell differentiation (Valeyev *et al.*, 2010; Hong *et al.*, 2011), and regulatory T cell-mediated suppression (Feinerman *et al.*, 2010; Almeida *et al.*, 2012). Further development of models and experiments may effectively reveal the regulatory mechanisms of the immune response by skin-homing and circulating lymphocytes and keratinocytes.

Identifying therapeutic targets

The modeling approach provides logical and mechanistic ways to identify new therapeutic targets by revealing

disease-related mechanisms and determining the possible effects of a therapeutic intervention that act on critical points to normalize the dysregulation of the system. Although not discovered by the modeling approach, cyclosporin is a drug that normalizes the dysregulation of T cell-mediated immune response in autoimmune diseases by blocking the translocation of NFAT (nuclear factor of activated T-cells) to the nucleus in T cells to suppress the transcription of *IL2*, which is the key molecule for the positive feedback in T-cell activation as IL-2 production leads to the tissue damage in autoimmune disease (Sigal and Dumont, 1992; Ferraccioli *et al.*, 2005).

Classifying skin disease and identifying the common control mechanisms

Mathematical description of the spatial pattern of skin eruptions might help us understand the control mechanisms of skin diseases, in which the global pattern of skin eruption is important for diagnosis. For example, the typically observed pattern in erythema gyratum repens has been reproduced by a diffusion equation model (Gilmore, 2005). This may reveal the underlying molecular control mechanism of the pattern formation (Rogers and Schier, 2011). Similarities in the pattern of eruptions, observed in different diseases, may suggest common underlying molecular mechanisms. For example, Staphylococcal scaled skin syndrome and pemphigus foliaceus show similarities in their clinical and histological manifestations, attributable to the common molecular mechanism of Desmoglein-1 cleavage (Stanley and Amagai, 2006).

Using this approach, it might be possible to classify skin diseases by the underlying control mechanisms of the pattern formation, as revealed by mathematical modeling. A first step for this ambitious project would be to systematically analyze the patterns of eruptions of various skin diseases, and identify the clusters of eruptions with a common underlying control mechanism. This new classification may help to explain the different phenotypic manifestations of the same disease (Loscalzo *et al.*, 2007) and will also

allow mathematical models for a particular disease to be rationally extended to other diseases with common molecular mechanisms.

TOWARD SUCCESSFUL USE OF A MATHEMATICAL PERSPECTIVE IN SKIN RESEARCH

Skin research may provide a prototypic framework for the mathematical modeling approach that can be used in a wide range of biomedical fields, as skin has the advantage of accessibility compared with other organs and there is a wealth of accumulated knowledge about skin disease.

Main challenges

There are major challenges, for both experiments and modeling, toward the successful development of the modeling approach in skin research.

Complexity of the skin: difficulty of experimental measurements. Given the anatomical and functional complexity of the skin, it is challenging to establish feasible experimental systems to quantitatively measure the activity of the components that are modeled (Pasonen-Seppanen *et al.*, 2001). If all the regulatory mechanisms are confined to the epidermis, organotypic culture is the system to be used. Otherwise, samples from patients or animal disease models will be required. The proteins of the cornified layer of the epidermis can be analyzed by ELISA using tape stripping samples (Kezic *et al.*, 2012), or by proteomics (Broccardo *et al.*, 2011). Two-photon microscopy may provide data for cellular kinetics of lymphocytes in the skin (Egawa and Kabashima, 2011). The modeling approach may further promote the development of novel technologies for quantitative measurements. Studies on inflammatory skin disease require us to analyze the dynamic interaction between the epidermis/dermis and the immune system. Mathematical modeling will inevitably be effective for many immunological/dermatological problems, where there are no experimental means to precisely measure the activities of immune cells and the response of keratinocytes in a real-time manner.

Confirmation bias—a pitfall of the iterative approach by experiment and model. The second challenge addressed

here is fundamental in the modeling approach for complex biological problems—how to avoid *confirmation bias* when models are developed and when model results are compared with experimental results. Confirmation bias is defined as the seeking or interpreting of evidence in ways that are partial to existing beliefs, expectations, or a hypothesis in hand (Nickerson, 1998). It is a bias behind our research practice, not a statistical bias, and is introduced not only by our own nature but also by the peer review process (Goodyear-Smith *et al.*, 2012). This problem has never been discussed in the context of mathematical modeling as far as the authors know, although it is significantly relevant. The process of model validation harbors the risk of confirmation bias: if one pursues only the compatibility between experimental and model results, the original hypothesis can stand without scientific basis, leading to false-positive results. Confirmation bias can have an even larger impact in the iterative cycle of experiments and modeling, as it may affect the choice of components included in the model and the choice of experimental data to compare with the model results. This problem occurs because the number of components to be modeled should be severely limited compared with the number of molecules/cells involved in a disease process, and also because disease-related data are generally complex and multidimensional with many measurements. From a viewpoint of dynamical systems theory, this problem is deeply related to *model invalidation*, which emphasizes the importance of invalidating models, rather than validating them, by excluding models that are incompatible with available data (Anderson and Papachristodoulou, 2009).

To decrease the risk of confirmation bias, multiple models should be constructed and used depending on the experimental data available. Ideally, the models should not rely on the validation by experiments but serve for excluding unrealistic models and unnecessary experiments by model invalidation. Whenever possible, hypothesis-free and data-driven approach is also recommended to compare experimental and model results. Visualization of experimental data by multidimensional analysis may be useful for addressing the biological relevance of the findings.

Future perspectives

The modeling approach has a huge potential to strengthen the power of conventional experimental approaches in dermatology. The quantitative and predictive power of the mathematical sciences will allow skin research to fully benefit from quantitative measurements by experiments. Use of mathematical models to reveal the underlying mechanisms for dynamic disease processes, together with a systematic approach to the combination of qualitative/quantitative data, enhanced by future technological advances for experimental measurement, will advance skin research in the postgenomic era.

This article has provided a view on skin disease modeling mainly from a control engineering perspective. For more general discussions on the systems approach in medicine, see other reviews (Vodovotz *et al.*, 2008; Auffray *et al.*, 2009; Clermont *et al.*, 2009; Hunter and Viceconti, 2009; Popel and Hunter, 2009; Yu *et al.*, 2011). There have been many research activities using mathematical modeling in dermatology, including geometry-based models (O'Toole, 2010), diffusion-based models (Gilmore, 2005), finite element models (Flynn *et al.*, 2011), biophysical models (Ciarletta *et al.*, 2011), and chemical reaction network models (Valeyev *et al.*, 2010; Tanaka *et al.*, 2011).

The most important initial step for successful application of mathematical modeling to skin disease is continuous and constant interaction between researchers in dermatology and those in engineering and physical sciences, and thus skin researchers are encouraged to be involved in cross-disciplinary research (Goldsmith, 2012). Nonbiological disciplines currently involved in cross-disciplinary research in biomedicine include engineering, mathematics, statistics, physics, chemistry, and computer science. The best mixture of expertise from different disciplines varies depending on the nature of the biological problem. In order to obtain findings that enrich basic and clinical dermatology, skin biologists and dermatologists are needed to drive and orient the cross-disciplinary research to address the most fundamental biological and medical problems.

CONFLICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGMENTS

We thank Professor A Hovnanian, Professor A Irvine, Dr S Kezic, Dr A Kubo, Dr R O'Shaughnessy, Dr Georgios Stamatas, and Professor K Parker for critical reading of the manuscript. RJT acknowledges the funding from the Engineering Physical Sciences Research Council through a Career Acceleration Fellowship. MO is a Human Frontier Science Program Long-Term Fellow.

REFERENCES

- Al-Nuaimi Y, Baier G, Watson RE *et al.* (2010) The cycling hair follicle as an ideal systems biology research model. *Exp Dermatol* 19:707–13
- Al-Nuaimi Y, Goodfellow M, Paus R *et al.* (2012) A prototypic mathematical model of the human hair cycle. *J Theor Biol* 310:143–59
- Almeida AR, Amado IF, Reynolds J *et al.* (2012) Quorum-sensing in CD4(+) T cell homeostasis: a hypothesis and a model. *Front Immunol* 3:125
- Anderson J, Papachristodoulou A (2009) On validation and invalidation of biological models. *BMC Bioinformatics* 10:132
- Auffray C, Chen Z, Hood L (2009) Systems medicine: the future of medical genomics and healthcare. *Genome Med* 1:2
- Bos JD, de Rie MA, Teunissen MB *et al.* (2005) Psoriasis: dysregulation of innate immunity. *Br J Dermatol* 152:1098–107
- Briot A, Deraison C, Lacroix M *et al.* (2009) Kallikrein 5 induces atopic dermatitis-like lesions through PAR2-mediated thymic stromal lymphopoietin expression in Netherton syndrome. *J Exp Med* 206:1135–47
- Broccardo CJ, Mahaffey S, Schwarz J *et al.* (2011) Comparative proteomic profiling of patients with atopic dermatitis based on history of eczema herpeticum infection and Staphylococcus aureus colonization. *J Allergy Clin Immunol* 127:186–93. 93 e1–11
- Cambiano V, Phillips AN (2011) Modelling the impact of treatment with individual antiretrovirals. *Curr Opin HIV AIDS* 6:124–30
- Cho K, Shin S (2003) Experimental design in systems biology, based on parameter sensitivity analysis using a Monte Carlo method: a case study for the TNF α -mediated NF- κ B signal transduction pathway. *Simulation* 79:726–39
- Ciarletta P, Foret L, Ben Amar M (2011) The radial growth phase of malignant melanoma: multi-phase modelling, numerical simulations and linear stability analysis. *J R Soc Interface* 8:345–68
- Clermont G, Auffray C, Moreau Y *et al.* (2009) Bridging the gap between systems biology and medicine. *Genome Med* 1:88
- Cork MJ, Danby SG, Vasilopoulos Y *et al.* (2009) Epidermal barrier dysfunction in atopic dermatitis. *J Invest Dermatol* 129:1892–908
- Denda M, Sato J, Tsuchiya T *et al.* (1998) Low humidity stimulates epidermal DNA synthesis and amplifies the hyperproliferative response to barrier disruption: implication for seasonal exacerbations of inflammatory dermatoses. *J Invest Dermatol* 111:873–8
- Egawa G, Kabashima K (2011) Skin as a peripheral lymphoid organ: revisiting the concept of skin-associated lymphoid tissues. *J Invest Dermatol* 131:2178–85
- Feinerman O, Jentsch G, Tkach KE *et al.* (2010) Single-cell quantification of IL-2 response by effector and regulatory T cells reveals critical plasticity in immune response. *Mol Syst Biol* 6:437
- Ferraccioli GF, Tomietto P, De Santis M (2005) Rationale for T cell inhibition by cyclosporin A in major autoimmune diseases. *Ann N Y Acad Sci* 1051:658–65
- Flynn C, Taberner A, Nielsen P (2011) Modeling the mechanical response of in vivo human skin under a rich set of deformations. *Ann Biomed Eng* 39:1935–46
- Fujii H, Arakawa A, Kitoh A *et al.* (2011) Perturbations of both nonregulatory and regulatory FOXP3+ T cells in patients with malignant melanoma. *Br J Dermatol* 164:1052–60
- Garny A, Noble D, Kohl P (2005) Dimensionality in cardiac modelling. *Prog Biophys Mol Biol* 87:47–66
- Gilmore S (2005) Modelling skin disease: lessons from the worlds of mathematics, physics and computer science. *Australas J Dermatol* 46:61–9
- Goldsmith LA (2012) Ensuring dermatology's future. *J Invest Dermatol* 132:747–50
- Goodyear-Smith FA, van Driel ML, Del Mar C *et al.* (2012) Analysis of decisions made in meta-analyses of depression screening and the risk of confirmation bias: a case study. *BMC Med Res Methodol* 12:76
- Grabe N, Neuber K (2007) Simulating psoriasis by altering transit amplifying cells. *Bioinformatics* 23:1309–12
- Hallou J, Bernard BA, Loussouarn G *et al.* (2000) Modeling the dynamics of human hair cycles by a follicular automaton. *Proc Natl Acad Sci USA* 97:8328–33
- Hirata Y, Akakura K, Higano CS *et al.* (2012) Quantitative mathematical modeling of PSA dynamics of prostate cancer patients treated with intermittent androgen suppression. *J Mol Cell Biol* 4:127–32
- Hong T, Xing J, Li L *et al.* (2011) A mathematical model for the reciprocal differentiation of T helper 17 cells and induced regulatory T cells. *PLoS Comput Biol* 7:e1002122
- Hunter P, Viceconti M (2009) The VPH-Physiome project: standards and tools for multiscale modeling in clinical applications. *IEEE Rev Biomed Eng* 2:40–53
- Ideker T, Galitski T, Hood L (2001) A new approach to decoding life: systems biology. *Annu Rev Genomics Hum Genet* 2:343–72
- Iizuka H, Honda H, Ishida-Yamamoto A (1997) Epidermal remodeling in psoriasis (II): a quantitative analysis of the epidermal architecture. *J Invest Dermatol* 109:806–10
- Jepps OG, Dancik Y, Anissimov YG *et al.* (2013) Modeling the human skin barrier - towards a better understanding of dermal absorption. *Adv Drug Deliv Rev* 65:152–68
- Kezic S, O'Regan GM, Lutter R *et al.* (2012) Filaggrin loss-of-function mutations are associated with enhanced expression of IL-1 cytokines in the stratum corneum of patients with atopic dermatitis and in a murine model of filaggrin deficiency. *J Allergy Clin Immunol* 129:1031–9. e1
- Kirschner DE, Chang ST, Riggs TW *et al.* (2007) Toward a multiscale model of antigen presentation in immunity. *Immunol Rev* 216: 93–118
- Leung DY (2000) Atopic dermatitis: new insights and opportunities for therapeutic intervention. *J Allergy Clin Immunol* 105: 860–76
- Loscalzo J, Kohane I, Barabasi AL (2007) Human disease classification in the postgenomic era: a complex systems approach to human pathology. *Mol Syst Biol* 3:124
- Loser K, Mehling A, Loeser S *et al.* (2006) Epidermal RANKL controls regulatory T-cell numbers via activation of dendritic cells. *Nat Med* 12:9
- Lowes MA, Bowcock AM, Krueger JG (2007) Pathogenesis and therapy of psoriasis. *Nature* 445:866–73
- Luo R, Cannon L, Hernandez J *et al.* (2011) Controlling the evolution of resistance. *J Process Control* 21:367–78
- Machado D, Costa RS, Rocha M *et al.* (2011) Modeling formalisms in Systems Biology. *AMB Express* 1:45
- Materi W, Wishart DS (2007) Computational systems biology in drug discovery and development: methods and applications. *Drug Discov Today* 12:295–303
- Nestle FO, Di Meglio P, Qin JZ *et al.* (2009) Skin immune sentinels in health and disease. *Nat Rev Immunol* 9:91
- Nickerson RS (1998) Confirmation bias: a ubiquitous phenomenon in many guises. *Rev Gen Psychol* 2:175–220
- O'Toole EA (2010) Molecular biology. In: *Rook's Textbook of Dermatology*. Burns T, Breathnach S, Cox N *et al.* (eds) Wiley-Blackwell: Oxford, UK, 1–22
- Onsum M, Rao CV (2007) A mathematical model for neutrophil gradient sensing and polarization. *PLoS Comput Biol* 3:e36
- Pasonen-Seppanen S, Suhonen TM, Kirjavainen M *et al.* (2001) Formation of permeability barrier in epidermal organotypic culture for studies on drug transport. *J Invest Dermatol* 117:1322–4
- Pastore S, Mascia F, Mariani V *et al.* (2008) The epidermal growth factor receptor system in skin repair and inflammation. *J Invest Dermatol* 128:1365–74
- Perera GK, Di Meglio P, Nestle FO (2012) Psoriasis. *Annu Rev Pathol* 7:385–422
- Plikus MV, Baker RE, Chen CC *et al.* (2011) Self-organizing and stochastic behaviors during the regeneration of hair stem cells. *Science* 332:586–9

- Popel AS, Hunter PJ (2009) Systems biology and physiome projects. *Wiley Interdiscip Rev Syst Biol Med* 1:153–8
- Rattenholl A, Steinhoff M (2003) Role of proteinase-activated receptors in cutaneous biology and disease. *Drug Dev Res* 59:408–16
- Rogers KW, Schier AF (2011) Morphogen gradients: from generation to interpretation. *Annu Rev Cell Dev Biol* 27:377–407
- Sakaguchi S, Yamaguchi T, Nomura T *et al.* (2008) Regulatory T cells and immune tolerance. *Cell* 133:775–87
- Sigal NH, Dumont FJ (1992) Cyclosporin A, FK-506, and rapamycin: pharmacologic probes of lymphocyte signal transduction. *Annu Rev Immunol* 10:519–60
- Stanley JR, Amagai M (2006) Pemphigus, bullous impetigo, and the staphylococcal scalded-skin syndrome. *N Engl J Med* 355:1800–10
- Stenn KS, Paus R (2001) Controls of hair follicle cycling. *Physiol Rev* 81:449–94
- Strange A, Capon F, Spencer CC *et al.* (2010) A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. *Nat Genet* 42: 985–90
- Strohman R (2002) Maneuvering in the complex path from genotype to phenotype. *Science* 296:701–3
- Tanaka RJ, Ono M, Harrington HA (2011) Skin barrier homeostasis in atopic dermatitis: feedback regulation of kallikrein activity. *PLoS One* 6:e19895
- Thomas-Vaslin V, Altes HK, de Boer RJ *et al.* (2008) Comprehensive assessment and mathematical modeling of T cell population dynamics and homeostasis. *J Immunol* 180:2240–50
- Uitto J, Christiano AM, McLean WH *et al.* (2012) Novel molecular therapies for heritable skin disorders. *J Invest Dermatol* 132:820–8
- Valeyev NV, Hundhausen C, Umezawa Y *et al.* (2010) A systems model for immune cell interactions unravels the mechanism of inflammation in human skin. *PLoS Comput Biol* 6:e1001024
- Vodovotz Y, Csete M, Bartels J *et al.* (2008) Translational systems biology of inflammation. *PLoS Comput Biol* 4:e1000014
- Voegeli R, Rawlings AV, Breternitz M *et al.* (2009) Increased stratum corneum serine protease activity in acute eczematous atopic skin. *Br J Dermatol* 161:70–7
- Yu T, Lloyd CM, Nickerson DP *et al.* (2011) The physiome model repository 2. *Bioinformatics* 27:743–4